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CYTODYNAMIC PROPERTIES OF HUMAN ENDOMETRIUM*

I. Cultivation in Fluid Media; Effects of Different Oxygen Tensions, Hydrogen Ion Concentrations, and Temperatures

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OUR fragmentary knowledge of the elements which make up the human organism can be attributed to the necessity for classical histologists to study the form and to overlook the function of cells, or to attempt to interpret dead, stained cells in terms of function. Fixed and stained cells and tissues are static objects, divorced from their environment, and robbed of functional activity. They are removed from both space and time, and are inanimate bodies lacking reality.

It is recognized that cells are functionally dependent directly upon their environment. Cells and environment form an inseparable physiologic continuity which equals life. As Carrel¹ pointed out, "A cell depends as strictly upon its medium as the nucleus upon the cytoplasm." Claude Bernard,² in demonstrating the importance of the *milieu intérieur*, showed that function is based on the chemical make-up of the internal environment or organic medium. The medium is synthesized by the cells and in turn regulates their physiologic action. The morphologic and cytodynamic, or functional, state of the cells depends upon the chemical constitution of the surrounding medium. Since each cell type, whether connective tissue or epithelium, responds in its own characteristic fashion to a similar environment, it can be assumed that the structural

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and functional states of a cell depend on its genetic constitution as well as on the physicochemical conditions of its medium. Therefore, it is only when the *milieu intérieur* is specifically defined that the morphologic description of a given type of cells acquires its full significance. Purely cytomorphicologic concepts removed from their media are abstract, and a system must be substituted which will embrace both the cell and medium in a cytodynamic aggregate.

Granted that structure and function are interdependent, it is logical to assume that each morphologic component of a cell possesses its own functional characteristics. It is through the integrated function of these morphologic parts that life is made possible. When cellular elements are looked upon only as structural units, they are separated from all of the dynamic properties that enable them to act as a functional whole. In the organism, different cells are endowed with specific properties. In turn, these properties may be altered by changes in the internal environment, such as results from inflammation, regeneration, or neoplasia. Conversely, any change in structure means an alteration in function—they are inseparable entities constituting a cytodynamic system. To quote Carrel again, "The conception of the cells and of the tissues, which I propose to substitute for the classical one, is that of a system cells-environment, of which the structural, functional, physical, physico-chemical and chemical conditions are considered in time as well as in space."

Applying Carrel's "new" concept of cytology required a different approach. This new method consists of a series of techniques, through which cytodynamics is comprehended in both its structural and functional aspects. Based on the ability of cells to remain viable *in vitro* when provided with proper physical and chemical conditions, tissue culture makes it possible to keep tissues alive indefinitely. Thus cells and tissues may be studied not only as morphologic entities but as synthesizers capable of developing, maturing, aging, and resisting or succumbing to disease-producing agents.

Although observations on morphologic pathology fill many volumes, the cytodynamic action of disease-producing agents and the significance of the changes appearing in the diseased cells remain obscure. This may be attributed to the fact that cellular pathology, like histology, has been based solely on structure. The reaction of an organism to a disease process cannot be understood so long as one considers cells as mere structural entities. However, if one views functional properties of cells as influenced by disease-producing agents in the *milieu intérieur*, the cellular doctrine of Virchow can be re-evaluated and possibly revived.

Because tissue culture provides a tool whereby cells and tissues are not elements of a dead body but living structures which were parts of more complex organisms, this study was undertaken to determine some properties of the cells which make up the endometrium through employment of the cytodynamic or "system cells-environment concept." This and subsequent papers will describe the application of different tissue-culture methods to the study of human endometrium and will record the observations thus made possible.

Methods

The choice of a tissue-culture method depends upon the problems to be investigated. Once the latter are well defined, the proper technique is easily determined.

The procedures available for tissue cultivation may be divided roughly into six general classes: (a) hanging-drop cultures of Carrel,³ Lewis and Lewis,⁴ and Maximow⁵; (b) open watch-glass method of Fell⁶; (c) flask method of Carrel⁷; (d) roller-tube method of Gey⁸; (e) fluid-medium method of Parker,⁹ and Medawar¹⁰; (f) organ-culture methods of Carrel and Lindbergh,¹¹ and Werthessen.¹²

The hanging-drop method is best suited for the cytologic examination of cells growing *in vitro* since their behavior may be followed for a prolonged period if the nutrient is changed every forty-eight to seventy-two hours.

The open watch-glass method facilitates the use of relatively large amounts of tissue and nutrient and is technically simple. However, this technique makes it difficult to control the gas requirements of the tissues and does not permit prolonged observation of their morphologic behavior.

The flask method permits cultivation of large tissue volumes under physiologic conditions, while nutrient and gas requirements can be accurately controlled. With this technique, microscopic scrutiny of the living cells is possible under any desired magnification.

The roller-tube method makes use of standard 16 by 150 mm. Pyrex test tubes, as many as 20 to 30 separate cultures can be planted in each tube. Four or five such tubes are equivalent to fifty to one hundred hanging-drop preparations or to a dozen or more Carrel flasks. Both the nutrient and gas requirements can be accurately controlled. However, the curvature of the tubes precludes good microscopic observation and high power photomicrography is difficult.

The fluid-medium method permits the storage of large quantities (100 mg.) of adult tissues in a state of functional survival for limited periods. Tissue fragments may be removed at any time during the experiment and examined microscopically.

Organ culture offers a technique whereby whole organs can be maintained in a perfusion apparatus so that growth of the organ as well as tissue repair can be observed. Biopsies may be taken and the effects of different substances upon the organ can be studied.

Parker's⁹ and Medawar's¹⁰ fluid media were employed for the maintenance of endometrium in a living differentiated state. This choice permitted simultaneous study of the effect of the endometrium upon the medium and of the medium upon the endometrium. Since neither Parker nor Medawar reported the use of his technique in the cultivation of human endometrium, a series of experiments were done to determine if these methods were applicable to the problem of maintaining the endometrium in a state of functional survival.

Endometrium, obtained by curettage, was cut into small uniform fragments (1 mm. sq.) and washed in Tyrode's solution (without the bicarbonate) to remove blood and other debris. To insure against contamination during preparation of the tissues, 250 units per milliliter of penicillin and 2 mg. per milliliter of streptomycin were added to the washing solution. After several changes of solution, 75 to 100 fragments of the tissue were transferred to 60-ml. Erlenmeyer flasks containing 2 ml. of medium. The flasks were gassed with varying mixtures of carbon dioxide, oxygen, and nitrogen, tightly sealed, and incubated at 37° C.

The nutrients used were (1) Parker's medium consisting of equal parts of (a) human cord serum 1 part, Tyrode's solution 3 parts, (b) 2 parts of Tyrode's solution with 4 Gm. of glucose per 1,000 ml., 1 part of 1.4 per cent isotonic sodium bicarbonate solution; (2) Medawar's medium consisting of 8 parts of Krebs-Ringer's bicarbonate solution containing defibrinated whole blood diluted with 4 times its volume of clear serum, and 1 part of 5 per cent glucose in water.

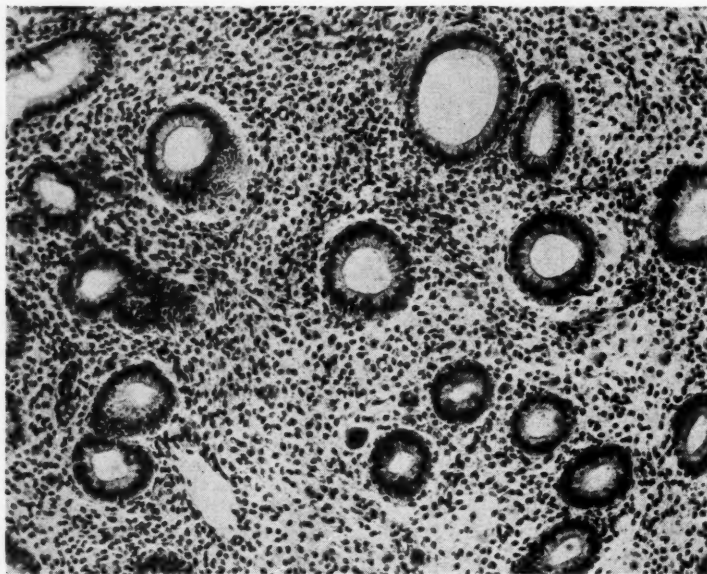


Fig. 1.—Stained section from fragment of mid-proliferative endometrium cultivated for seven days in Parker's medium. Culture gassed with 80 per cent oxygen, 5 per cent carbon dioxide, and 15 per cent nitrogen. Formalin fixative, hematoxylin-eosin stain.

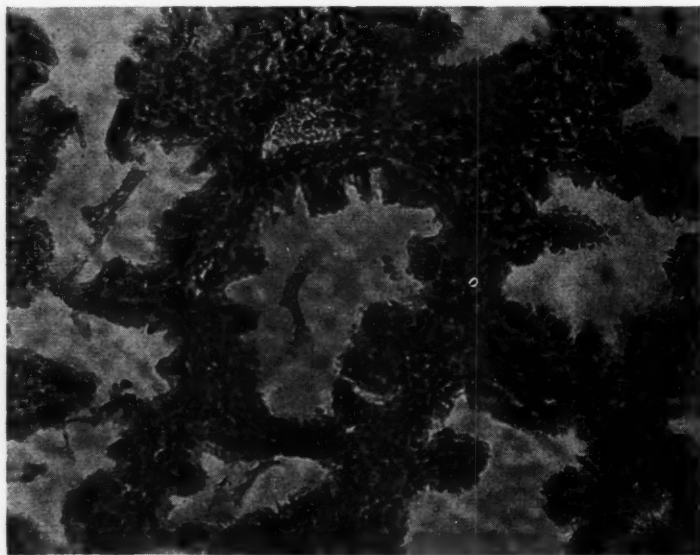


Fig. 2.—Stained section from fragment of secretory endometrium cultivated for seven days in Parker's medium. Culture gassed with 80 per cent oxygen, 5 per cent carbon dioxide, and 15 per cent nitrogen. Formalin fixative, hematoxylin-eosin stain.

Proliferative and secretory endometrium cultivated in such fluid media for seven days exhibited no alteration in cellular morphology. The proliferative, or interval-phase, endometrium contained well-preserved glands whose epithelium was columnar and showed a number of mitotic figures (Fig. 1). The secretory, or progestational, endometrium demonstrated the characteristic corkscrew pattern of the glands with the epithelium exhibiting tuftlike accumulations in cross section (Fig. 2).

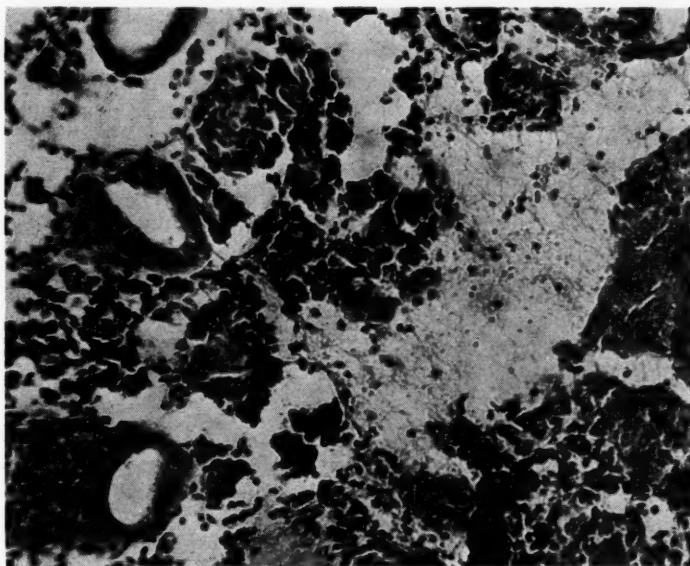


Fig. 3.—Stained section from fragment of mid-proliferative endometrium cultivated for seven days in Parker's medium. Culture gassed with 10 per cent oxygen, 5 per cent carbon dioxide, and 85 per cent nitrogen. Formalin fixative, hematoxylin-eosin stain. (Compare with Fig. 1.)

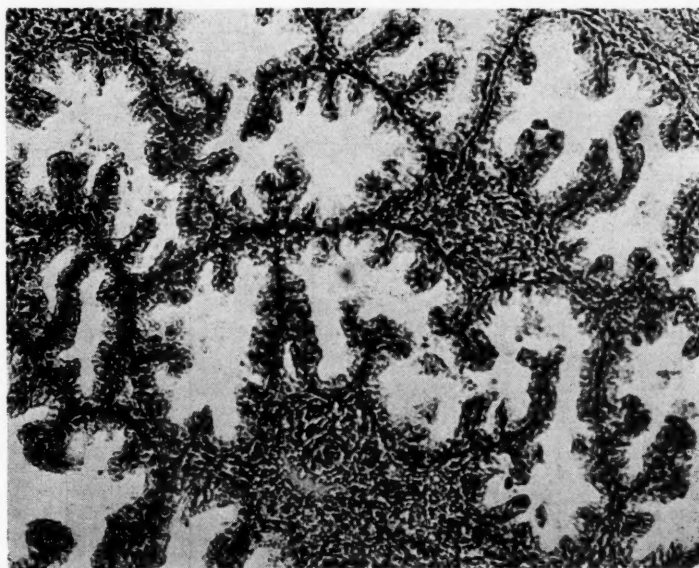


Fig. 4.—Stained section from fragment of secretory endometrium cultivated for seven days in Parker's medium. Culture gassed with 10 per cent oxygen, 5 per cent carbon dioxide, and 85 per cent nitrogen. Formalin fixative, hematoxylin-eosin stain.

Parker's and Medawar's media both proved satisfactory for maintenance of the endometrium, the only difference being that in the latter more mitotic figures were present in the interval endometrium. In no instance were mitotic figures seen in the secretory endometrium.

Effect of Varied Gas Tensions

The discovery by Parker⁹ that most adult tissues require more oxygen to maintain growth and functional activity than do embryonal tissue suggested that the oxygen demands of proliferative and secretory endometrium might be different. Sister cultures maintained anaerobically and in atmospheres containing 10 per cent, 20 per cent, 40 per cent, 80 per cent, and 95 per cent oxygen were studied. In these experiments the carbon dioxide was held constant at 5 per cent whereas the nitrogen was varied inversely with the oxygen. The cultures were gassed daily for five minutes for the duration of the experiment (seven days). Eighty per cent and 95 per cent oxygen provided the best cell preservation in both proliferative and secretory endometria (Table I). At

TABLE I. THE EFFECT OF DIFFERENT OXYGEN TENSIONS ON THE CULTIVATION OF ENDOMETRIUM IN FLUID MEDIUM

PHASE OF ENDOMETRIUM	GAS MIXTURE			HISTOLOGIC APPEARANCE OF TISSUE
	O ₂ %	CO ₂ %	N%	
Proliferative	0	5	95	Marked necrosis
Proliferative	10	5	85	Marked necrosis
Proliferative	20	5	75	Marked necrosis
Proliferative	40	5	55	Some central necrosis
Proliferative	80	5	15	Normal
Proliferative	95	5	0	Normal
Secretory	0	5	95	Normal
Secretory	10	5	85	Normal
Secretory	20	5	75	Normal
Secretory	40	5	55	Normal
Secretory	80	5	15	Normal
Secretory	95	5	0	Normal

TABLE II. HYDROGEN ION CONCENTRATION OF THE MEDIUM AT THE BEGINNING AND TERMINATION OF THE EXPERIMENT

PHASE OF ENDOMETRIUM	GAS MIXTURE			pH MEDIUM AT START	pH MEDIUM AT END	HISTOLOGIC APPEARANCE OF TISSUE
	CO ₂ %	O ₂ %	N%			
Proliferative	1	60	39	7.4	7.6	Normal
Proliferative	2	60	38	7.4	7.4	Normal
Proliferative	5	60	35	7.4	7.3	Normal
Proliferative	10	60	30	7.4	6.9	Necrosis
Proliferative	15	60	25	7.4	6.9	Necrosis
Proliferative	20	60	20	7.4	6.7	Necrosis
Proliferative	25	60	15	7.4	6.6	Necrosis
Proliferative	30	60	10	7.4	6.5	Necrosis
Proliferative	35	60	5	7.4	6.3	Necrosis
Secretory	1	60	39	7.4	7.6	Some necrosis
Secretory	2	60	38	7.4	7.4	Some necrosis
Secretory	5	60	35	7.4	7.3	Some necrosis
Secretory	10	60	30	7.4	6.9	Normal
Secretory	15	60	25	7.4	6.9	Normal
Secretory	20	60	20	7.4	6.7	Normal
Secretory	25	60	15	7.4	6.6	Necrosis
Secretory	30	60	10	7.4	6.5	Necrosis
Secretory	35	60	5	7.4	6.3	Necrosis

lower oxygen concentrations, proliferative endometrium showed almost complete degeneration and necrosis (Fig. 3), while secretory endometrium, even under anaerobic conditions showed no alteration in morphology (Fig. 4).

Effect of Varied pH

In the cultivation of large amounts of tissue, the maintenance of proper pH in the medium is essential. Since different physiologic phases of the endometrium varied in their oxygen requirements, studies were made to determine the optimal pH for successful cultivation of the tissue. Since the media used contained sodium bicarbonate, the pH range could be controlled by introducing carbon dioxide. Cultures were gassed daily for three days with varying concentrations of carbon dioxide. The amount of gas delivered to each flask was approximately 2.5 liters per day. At the termination of the experiment the fluid medium was removed and the pH determinations made under oil using a Beckman pH meter. The tissue fragments were fixed in 10 per cent formalin, stained with hematoxylin and eosin, and examined microscopically.

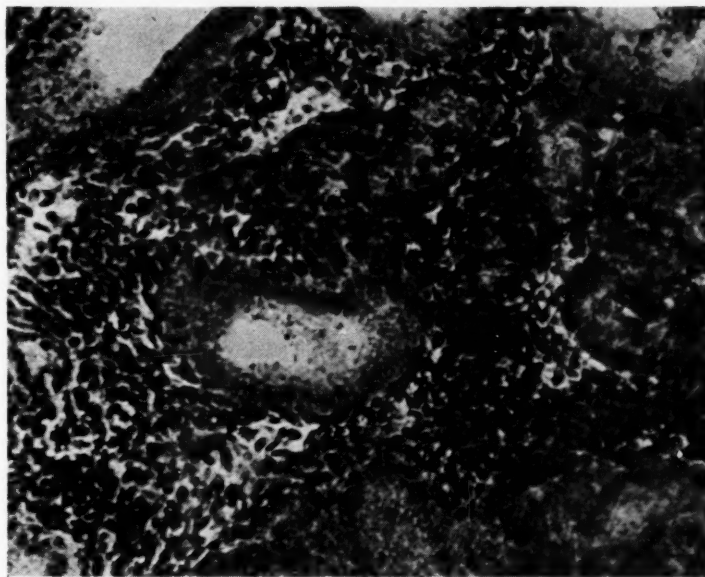


Fig. 5.—Stained section from fragment of mid-proliferative endometrium cultivated for fifteen days in Parker's medium at 37° C. Culture gassed with 80 per cent oxygen, 5 per cent carbon dioxide, and 15 per cent nitrogen. Formalin fixative, hematoxylin-eosin stain. (Compare with Fig. 1.)

Table II lists the pH values for the liquid media at the time of planting and after three days' cultivation. The pH of all media at the start was practically the same, namely, 7.4. After three days' cultivation the pH ranged from 6.3 to 7.6. Histologic sections of the cultivated fragments showed that the proliferative endometrium was best maintained at pH 7.3 to 7.6; the secretory endometrium at pH 6.7 to 6.9.

Effect of Varied Temperatures

The maintenance and cultivation of mammalian ovaries by Martinovitch¹³ and of adult mammalian skin and blood vessels by Hanks¹⁴ at temperatures several degrees below normal body temperature suggested the possibility that the endometrium might be similarly adaptable. These investigators showed

that organized tissues maintain their viability up to one hundred three days at subnormal temperatures (5° to 34° C.). The successful application of this discovery to the endometrium would enable one to maintain unlimited quantities of tissues for histologic, biochemical, or metabolic studies.

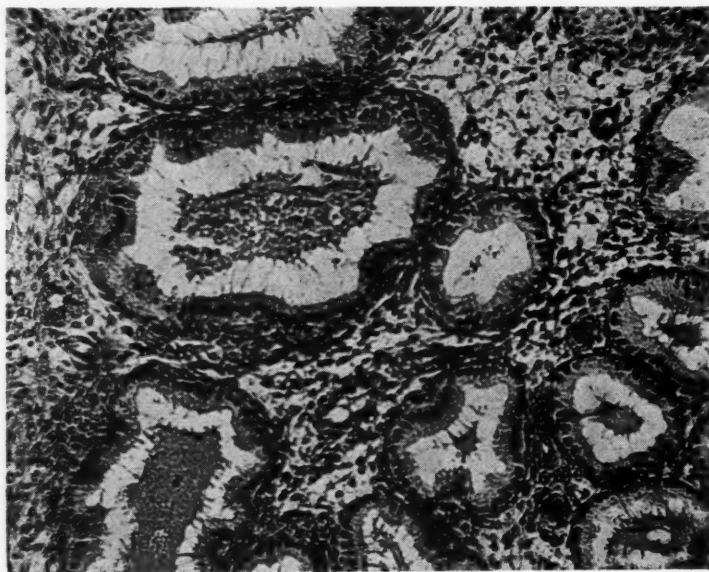


Fig. 6.—Stained section from fragment of secretory endometrium cultivated for thirty days in Parker's medium at 25° C. Culture gassed with 80 per cent oxygen, 5 per cent carbon dioxide, and 15 per cent nitrogen. Formalin fixative, hematoxylin-eosin stain. (Compare with Fig. 2.)

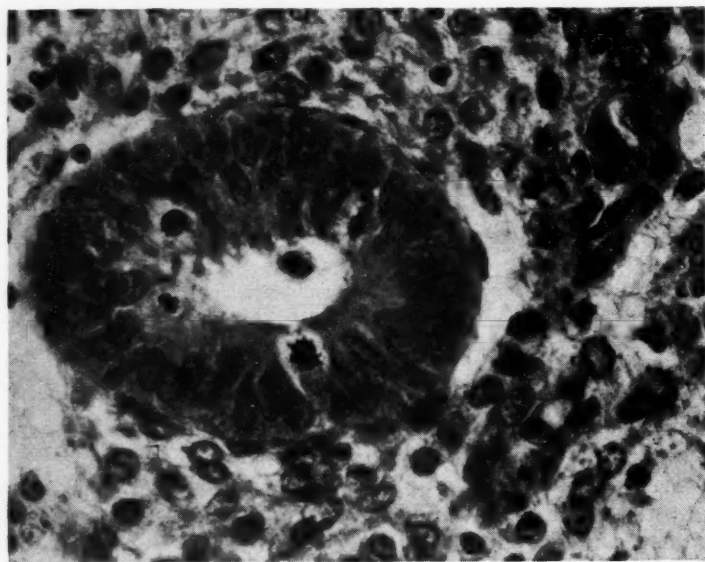


Fig. 7.—Stained section from fragment of mid-proliferative endometrium cultivated for thirty days in Parker's medium at 25° C. Culture gassed with 80 per cent oxygen, 5 per cent carbon dioxide, and 15 per cent nitrogen. Formalin fixative, hematoxylin-eosin stain. (Compare with Fig. 1.)

Cultures were incubated 4° to 5° , 25° , 34° , and 37° C. Sufficient phenol red was added to the medium to give a final concentration of 0.005 per cent for the detection of changes in pH. The control cultures incubated at 37° C. began

to show evidence of degenerative changes after ten days. The nuclei were either pyknotic or karyolytic and patches of necrosis were evident (Fig. 5). The endometrium (proliferative or secretory) maintained at subnormal temperatures after thirty-five days was histologically normal in appearance (Fig. 6). At 34° C. mitotic figures were prominent in the proliferative endometrium, while none was observed at 4° to 5° C. incubation (Fig. 7). The temperature experiment was terminated after thirty-five days, but judging from the normal appearance of the tissues it could have been continued longer.

Comment

The results here reported indicate that tissue-culture methods can well be applied to study of human endometrium. The ability to maintain endometrium in a viable state for prolonged periods provides an avenue of approach which enables one to study the simultaneous effect of the cells upon the medium and of medium upon the cells. Considering the endometrial response to hormonal stimuli, the use of tissue culture offers many possibilities for further study. A more direct approach can be used to determine the effect of specific substances on tissue cultivated in vitro since the environment can be so accurately controlled. By regulating physicochemical conditions such as osmotic tension, oxygen tension, and H-ion concentration, the tissue can be studied in media of unvarying composition. With the development of synthetic media, adult tissue may be studied in environments of known composition and the nutritional requirements determined. This presents interesting possibilities because we are still far from knowing how the medium determines functional activities and differentiation of main cell types. Amino acids, vitamins, hormones, oligodynamic inorganic ions, etc., supply tissues with the building blocks they require for growth, but how they are utilized in different manners by different cells is still a mystery. By using nutrient media of known composition and utilizing known methods of detect chemical changes, certain of these questions should be clarified.

Tissue culture offers a dynamic approach to many unsolved problems in gynecologic histology, since it is possible to determine the effect of hormonal *milieu intérieur* upon living cells. Classical histology has provided many abstractions which were of immense value in the development of our knowledge of the female genital tract, even though it has separated the cells from their environment and ignored their functional activity. In vitro techniques offer a means whereby structure and function may be correlated.

Summary

Utilizing the fluid-medium culture techniques of Parker and Medawar, human endometrium was maintained in a state of functional survival for a limited period (thirty-five days). Certain physicochemical requirements of proliferative and secretory endometria were noted. Proliferative endometrium was best maintained in an atmosphere containing a high oxygen tension (80 to 95 per cent), while secretory endometrium could be maintained at lower oxygen tensions and even anaerobically. Proliferative endometrium was best when the pH of the medium was within physiologic limits (pH 7.4) and secretory endometrium at pH 6.9. Cultivation of both proliferative and secretory endometria at subnormal temperatures (below 37° C.) prolonged the period of morphologic maintenance.

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(Part II of this study will appear in a later issue)

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THE LAURENCE-MOON-BIEDL SYNDROME: A CONFUSED SYMPTOM-COMPLEX*

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THE Laurence-Moon-Biedl syndrome, as it was described originally, included patients with congenital or heredofamilial hypogonadism, mental retardation, atypical retinitis pigmentosa, obesity, and skeletal deformities, specifically dwarfism and polydactylism. Many of the patients, with subsequent diagnoses under this category, have lacked varying numbers of these clinical characteristics. In fact, it has been said that only one of the extra-endocrine characteristics in combination with congenital hypogonadism permits diagnosis of the syndrome. This relaxation of diagnostic requirements removes any clinical differences between many patients, who are presumed to have the Laurence-Moon-Biedl syndrome, and those with congenital absence, aplasia, hypoplasia, or degeneration of the gonads³ including Turner's syndrome,⁴ ovarian agenesis,^{5, 6} and the syndrome described by Klinefelter, Reifenstein, and Albright.⁷ Furthermore, a critical assessment of the presumed hypogonadism of many of the patients who have been included under the Laurence-Moon-Biedl syndrome indicates that it was predicated frequently on the slightest provocation and that rarely was it diagnosed from definite objective data. The result is that the Laurence-Moon-Biedl syndrome constitutes a very confused symptom-complex.

Historical Review

Laurence and Moon in 1866¹ described four siblings, three males who were chronologically postpubescent and one female who was chronologically prepubescent. Being interested especially in ophthalmology, Laurence and Moon stressed the presence of atypical retinitis pigmentosa which was associated with shortness of stature, obesity, mental retardation, and an orthopedic deformity which caused these patients to have a peculiar gait. Polydactylism was present in one of the patients. Analysis of the description of the three postpubescent males supplies convincing evidence of hypogonadism. Hutchinson,⁸ ten years later, re-examined these patients and confirmed the findings of Laurence and Moon and, in addition, he made a diagnosis of hypogonadism in the female, who was then sixteen years of age and was apubescent. Accordingly, the pentad of congenital characteristics was established for these four patients.

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Attention to the syndrome represented by the four patients of Laurence and Moon was diverted, perhaps, by the report of Fröhlich⁹ of patients with hypogonadism and obesity, in association with intrasellar and parasellar tumors. Until 1920, the syndromes described by Laurence and Moon and by Fröhlich were confused commonly in the medical literature. Some of the clinical characteristics of the patients of Laurence and Moon were described in association with tumors of or about the pituitary, but all five of the characteristics were not described in patients with tumors of the pituitary or in the hypothalamic area. Bardet¹⁰ reported in 1920 a patient similar to the one of Laurence and Moon, who had no tumor of the pituitary or about it; however, he failed to describe any heredofamilial occurrence or mental deficiency.

Biedl² in 1922 reported two patients in brief abstract form; amplification of the data of these patients by Raab¹¹ in 1924 showed that they had the characteristics of the original patient of Laurence and Moon, save that mental deficiency was not emphasized. Solis-Cohen and Weiss¹² in 1925 recognized the symptom-complex of the patients of Laurence and Moon and of Biedl as a definite clinical entity and called it the Laurence-Moon-Biedl syndrome. Review studies by Reilly and Lisser¹³ in 1932, by Warkany, Frauenberger and Mitchell¹⁴ in 1937, by Sorsby, Avery and Cockayne¹⁵ in 1939 and by Anderson,¹⁶ of our group, with regard to histopathology in 1941 afford clinical data of previously reported patients and synthesize present consensus. A current report by Francke¹⁷ considers the gonads in the Laurence-Moon-Biedl syndrome.

Study of the data of these reviews and of individual reports of patients indicates that the list of congenital anomalies which have been described as concomitants of the Laurence-Moon-Biedl syndrome is long and includes the following: syndactylism, night blindness, nerve deafness, oxycephaly, bradycephaly, kyphoscoliosis, genu valgum, congenital heart disease, dwarfing of stature, coxa vara, ataxia, nystagmus, strabismus, pes planus, gynecomastia, scanning speech, various disturbances of gait, hydrocephalus, ptosis of the eyelids, facial palsy, lordosis, cyanosis, and adiposis dolorosa.

Many attempts have been made to offer a single etiological explanation of the syndrome. Biedl² suggested that it might be due to a familial cerebral anomaly. Raab's concept¹¹ was a disorder of the relationship of the pituitary and hypothalamus, associated with a massive, high dorsum sellae. Ornstein¹⁸ postulated a developmental defect of the ectopic zone of the prosencephalon and related the skeletal abnormalities to an accidental coupling of defective somatic genotypic characters. This theory was challenged on the ground that polydactyly probably occurred too frequently to be explained as a chance coupling. As Anderson¹⁶ observed in 1941, much of the unsatisfactory theorizing could be attributed to the fact that an autopsy was not done on a patient with the syndrome until 1936. He found from the study of the material of six autopsies, the total number of complete ones reported including that on his patient, that three of the six patients showed "some abnormality" in the pituitary and that "the findings in the hypothalamus have not been remarkable." Although the autopsy on his 15-year-old male patient showed a "striking predominance" of basophilic cells, the histology of the testes was essentially normal, despite a description of slight penile hypoplasia and hypospadias. (We suggest that, had the presumed hypogonadism of many patients been objectively established and subsequently qualified in terms of urinary hormone levels and gonadal histopathology, theories would have been oriented by a more complete understanding of the gonadal phase.) Warkany, Frauenberger, and Mitchell¹⁴ accepted the existence of the five cardinal characteristics in only twenty-four of the eighty-seven patients reported in the literature. Warkany and Weaver,¹⁹ pointing out that more individuals had "in-

complete," "transitional," or "multiplied" forms of the syndrome than those who had the classical pentad of characteristics, questioned the likelihood that the syndrome represented a clinical entity and suggested that it represents no more than a combination of more or less frequently occurring heredofamilial deviations.

Clinical Data

In view of the fact that we have seen three female patients who showed the other classical characteristics of the Laurence-Moon-Biedl syndrome, despite the absence of hypogonadism, and of the fact that these patients previously had the diagnosis of the Laurence-Moon-Biedl syndrome, the records of these patients are reported.

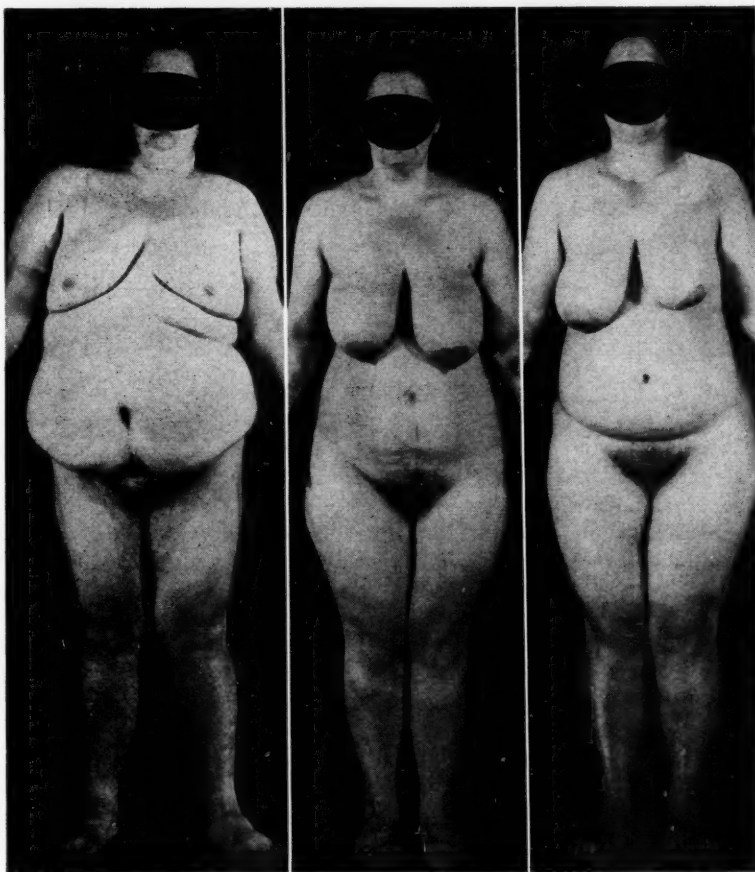


Fig. 1.—Left to right, Cases 1, 2, and 3, respectively.

CASE 1.—This was a white, single, nulliparous woman, aged 22 years, with mental deficiency and obesity and a history of headaches and low abdominal pain. Since infancy, she had been unable to see anything except large objects. The obesity had been progressive since the first year of age. Bilateral extra toes were removed at 7 years of age. Pubescence began at 14 years of age and was normal, culminating in menarche at 15 years of age. Subsequently, menses have recurred every 30 to 90 days, lasting 6 to 7 days and associated with moderate dysmenorrhea. The familial history included a high incidence of mental deficiency and obesity.

Pertinent physical findings (Figs. 1, 2, and 3) included the following: The weight was 215 pounds with a buffalo type of fat distribution. Ophthalmoscopic examination showed diffusely scattered corpuscular pigment throughout both retinal equators with an area of choroidal sclerosis around the left disc. There was bilateral syndactylism of hands and feet with scars of removed extra digits on the lateral surfaces of the fifth tarsal phalanges. Breasts were normal save for obesity and pendulosity. External and internal pelvic examination showed normal organs. The uterus was 3 inches in depth. Psychological data included an I. Q. of 56, according to the Wechsler-Bellevue scale.



Fig. 2.—Hands of Case 1.

Pertinent laboratory findings included the following: The basal metabolic rate was -6 per cent, serum cholesterol 270 mg. per cent, and the fasting blood sugar was 98 mg. per cent. Roentgenograms showed a normal sella turcica, failure of closure of the first sacral segment, destruction of both fifth metatarsals, and a marked hallux valgus deformity. Intravenous urograms showed an apparent anomaly of the calyces of the left kidney. An endometrial biopsy on the 26th day of the cycle showed an endometrium of early progestational therapy and equivalent to one of the 18th or 19th day of a normal 28-day cycle. Subsequently, and during the postovulatory plateau, studies of urinary gonadotropins were done. The values for these were less than 1 rat uterine unit per 24 hours. (The range of these values for normal women, according to our method, is 2 to 10 rat uterine units per 24 hours, the average being 5 rat uterine units. This value, accordingly, is lower than normal.) Studies of urinary 17-ketosteroids gave values of 3.92 mg. per 24 hours. (The range of normal by our method is 4 to 14 mg. per 24 hours for women. Accordingly, this value is normal.)

This patient, despite her various genetic anomalies, was established by tests to have normal ovarian function. The infrequency of menstruation of this patient certainly should not be advanced as evidence of hypogonadism.

CASE 2.—This is a white, married woman, aged 37 years and 5 months, para ii-0-ii, with mental deficiency of long standing, paranoid delusions, obesity, marked impairment of vision, and orthopedic anomalies. Pubescence had been normal, culminating in menarche at 12 years of age. The menstrual pattern had been normal and the patient had had two pregnancies, followed by normal deliveries. The heredofamilial element is supplied by the fact that a brother has impaired vision and polydactylism.

Pertinent physical findings (Figs. 1, 4, and 5) included the following: The obesity was generalized, weight being 168 pounds and height 62.5 inches. Ophthalmoscopic examination showed advanced retinitis pigmentosa with marked optic atrophy and attenuation of the retinal vessels. There were bilateral syndactylism of the third and fourth toes and

toelike appendages on the lateral surfaces of each fifth toe. The digits of the hands were extremely short and blunt. The breasts were normal, save for pendulosity. External and internal genital organs were normal save for a slight irregularity of the uterus.

Pertinent laboratory findings included the following: The basal metabolic rate was -11 per cent and glucose tolerance was normal. Studies of visual fields showed only central vision. Psychometric studies verified mental deficiency and assigned an I. Q. of 75. Roentgenograms of the sella turcica were normal.

The normal pubescence and subsequent menstrual function and the multiparity of this patient do not warrant a diagnosis of hypogonadism.

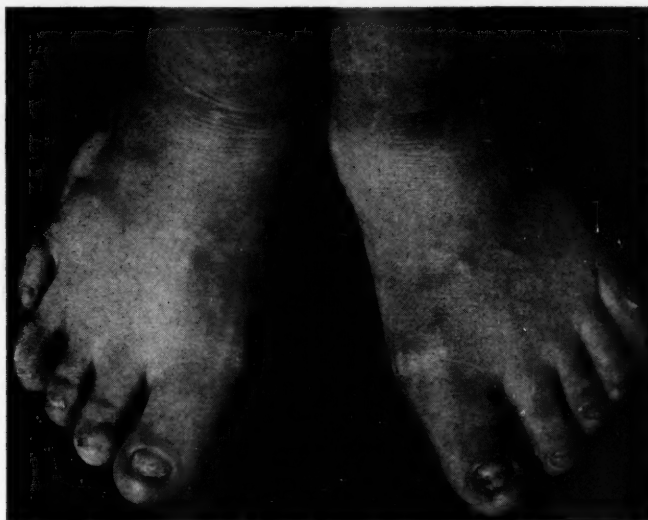


Fig. 3.—Feet of Case 1.

CASE 3.—This is a white, single, nulliparous woman, aged 31 years and 4 months, with mental deficiency, blindness, obesity, and diverse neurological symptoms including vasomotor instability, restlessness, and hyperkinesis. The patient had attended a school for the blind since the age of 10 years. Pubescence had been normal, culminating in menarche at 14 years of age. Her menstrual pattern had been normal, with flowing approximately every 30 days and of normal duration and amount. A subtotal thyroidectomy had been done at the age of 29 years because of presumed hyperthyroidism. The heredo-familial element is supplied by the facts that one brother is obese, blind, and has polydactyly, and another brother is obese, blind, markedly deficient in mentality, and has polydactyly.

Pertinent physical findings (Fig. 1) included the following: The obesity was generalized, weight being 173 pounds and height 64 inches. There was a constant lateral nystagmus and ophthalmoscopic examination showed retinitis pigmentosa with bilateral optic atrophy. There was a well healed thyroidectomy scar. The lateral aspects of each fifth toe were scarred from removal of supernumerary toes. The breasts were normal, save for striking disproportion. External and internal genital organs were normal.

Pertinent laboratory findings included the following: The basal metabolic rate was -8 per cent. Roentgenograms of the sella turcica were normal and of the feet showed bifid fifth metatarsals and small accessory bones, distally and laterally. Psychometric studies assigned a mental age of 13 years.

The normal pubescence and menstrual pattern, as well as the absence of any clinical evidence of hypogonadism, do not warrant a diagnosis of hypogonadism in this patient. As a matter of fact, if one were forced to make some

endocrinological correlation in these three patients, it might include the existence of sufficient enlargement of the thyroid glands of two of them to warrant thyroidectomy.



Fig. 4.—Hands of Case 2.

Our interest having been aroused by the nonexistence of any actual hypogonadism in these three patients, we reviewed the records of all patients with diagnoses of Laurence-Moon-Biedl syndrome since Duke Hospital was opened twenty years ago. During this time approximately 383,000 patients have been seen. In addition to the three patients reported, six other females with more or less complete extraendocrine characteristics of the Laurence-Moon-Biedl syndrome were found. In none of these was a diagnosis of hypogonadism justified. Patients for whom the diagnosis of Laurence-Moon-Biedl syndrome was suggested on even less critical data were not evaluated. Male as well as female patients were considered in this review of hospital admissions, but the present study deals only with females. One of the nine females had been reported by Arena²⁰ in 1937; at the age of 12 years, she was pubescent as judged by the mammary development shown in her photographs; accordingly, a diagnosis of hypogonadism is impossible. The pertinent data of the nine patients are summarized in Table I.

Having found no clear-cut hypogonadism of the Duke Hospital female patients with diagnoses of Laurence-Moon-Biedl syndrome, we proceeded to analyze the reports in the literature of females with this diagnosis. We considered the reports of thirty-six patients to provide adequate descriptions for fairly accurate analysis of ovarian function. Our analysis has considered the following: Prepubescent patients were excluded, if their chronologic ages were less than 15 years. The gonadal function of postpubescent patients was graded by over-all consideration of menstrual history, degree of development of the sexual system, obstetrical history, and the objective data of pelvic examinations. We could not accept diagnoses of hypogonadism in the literature, which were founded upon such unconvincing, diagnostic trivia as: scantiness of flowing, irregularities of cycle, childless mating, inability to palpate ovaries on bimanual examination, and the presence of an "intact hymen with unsatisfactory rectal examination." Eighteen of these thirty-six patients were excluded because they were chronologically prepubescent. Only eight of the remaining eighteen patients had all of the extraendocrine cardinal char-

acteristics of the syndrome. Only three of these eight patients apparently warranted diagnoses of clear-cut hypogonadism. In none of these patients had urinary hormonal values been established; therefore, the presumed hypogonadism could not be qualified as to its being hypergonadotropuric, hypogonadotropuric, or eugonadotropuric.



Fig. 5.—Feet of Case 2.

Since the first draft of our study was made, Francke¹⁷ has reported two female patients with all of the classical extraendocrine characteristics of the syndrome but without hypogonadism. One of the patients, aged 51 years, was six years postmenopausal. The other patient, aged 45 years, continued to have cyclic bleeding. Both patients were studied by determination of urinary gonadotropins, urinary 17-ketosteroids and urinary corticosteroids. The data of these two patients placed them in the eugonadotropuric group, accepting the postmenopausal hypergonadotropuria of one of these patients as physiologic.

TABLE I. SUMMARY OF THE DATA OF DUKE HOSPITAL FEMALE PATIENTS WITH THE DIAGNOSIS OF LAURENCE-MOON-BIEDL SYNDROME

	AGE (YEARS)	OBESITY	HYPOGO- NADISM	RETINITIS PIGMENTO- SA	MENTAL DEFICI- ENCY	FAMILIAL INCI- DENCE	SKELETAL ABNOR- MALITIES
Case 1	22	X	-	X	X	X	X
Case 2	37	X	-	X	X	X	X
Case 3	31	X	-	X	X	X	X
Case 4	30	X	-	-	X	X	X
Case 5	23	-	-	X	X	X	X
Case 6	13	X	-	X	X	X	-
Case 7	11	X	*	-	X	-	X
Case 8	7	X	**	-	X	-	X
Case 9 (Arena ²⁰)	12	X	**	X	X	X	X

X, positive history; - negative history; * prepubertal; ** pubescent.

Comment

Our data, combined with a critical analysis of cases reported of females who were presumed to have the Laurence-Moon-Biedl syndrome, indicate that the laxity of criteria regarded necessary for diagnosis has concerned not only

extraendocrine characteristics but also, and to an even greater degree, objective evidence of hypogonadism. This is pointed up by our acceptance of hypogonadism in only three female patients. Evidence has been submitted that the cardinal extraendocrine characteristics may occur in women with normal ovarian function and fertility. Some of these women by objective studies have been shown to have normal urinary hormonal values, including those for gonadotropins, that is, with eugonadotropuria.

Some of our group,^{3, 21} on several occasions, have drawn parallels between the extraendocrine characteristics of patients with congenital aplasia and hypoplasia of the ovaries, including those with ovarian agenesis and Turner's syndrome, and of patients presumed to have the Laurence-Moon-Biedl syndrome. The suggestion has been made that patients with the classical pentad of the Laurence-Moon-Biedl syndrome doubtless had congenital aplasia or hypoplasia of the ovaries and, therefore, would have hypergonadotropuria. If this were the case, then the Laurence-Moon-Biedl syndrome would become a subgroup of patients with congenital aplasia and hypoplasia of the ovaries. So far, no patient with classical manifestations of the Laurence-Moon-Biedl syndrome has been described to have hypergonadotropuria. Conversely, no patient, with congenital aplasia and hypoplasia of the ovaries and with hypergonadotropuria, has included all of the extraendocrine characteristics of the Laurence-Moon-Biedl syndrome, despite the fact that these patients are characterized by a diverse group of congenital anomalies.³ A brief list of some of these anomalies is given for comparison with those of the Laurence-Moon-Biedl syndrome: shortness of stature, mental retardation, deafness, cubitus valgus, internal strabismus, bilateral ptosis of the eyelids, myopia, webbed neck, coarctation of the aorta, underdevelopment of the jaw, osteoporosis, and absence of various epiphyses about the wrist and ankle.

No proof has been established that the hypogonadism which is associated with the classical Laurence-Moon-Biedl syndrome results in the female from deficient gonadotropic activity of the pituitary, as characterized by hypogonadotropuria.

Although we have not included data on male patients with Laurence-Moon-Biedl syndrome, presumed or classical, a brief and comparative consideration of the male seems desirable to amplify this discussion. In general, males with congenital aplasia, hypoplasia, and degeneration of the gonads, including so-called "prepuberal castrates,"²² and those of the syndrome described by Klinefelter, Reifenstein, and Albright,⁷ show far fewer extraendocrine anomalies than do females with congenital aplasia and hypoplasia of the ovaries. Accordingly, they do not suggest as close a parallelism to patients with the Laurence-Moon-Biedl syndrome as females.

A review of the male patients seen at Duke Hospital with presumed or classical Laurence-Moon-Biedl syndrome showed the same laxity in the diagnosis of the syndrome and of the associated hypogonadism as was encountered in the review of the females. Comparable to our experience with the females, we have seen and studied two postpubescent males with all of the extraendocrine characteristics of the syndrome, but without clinical evidence of hypogonadism. The urinary values for gonadotropins and 17-ketosteroids of these patients were normal. No males with the classical syndrome have been proved to have hypergonadotropuria or hypogonadotropuria.

Roth²³ studied four male patients, whom he accepted as representing the Laurence-Moon-Biedl syndrome, despite the fact that they lacked mental retardation, polydactylism or syndactylism, and retinitis pigmentosa. The hypogonadism of these patients was related by urinary gonadotropin studies and by studies of testicular biopsies to hypogonadotropic function of the pituitary.

Francke¹⁷ reported the case of a man, 45 years old, with all of the characteristics of the Laurence-Moon-Syndrome save for absence of polydactylism. Urinary hormone studies were not done. A partial autopsy revealed testicular histopathology quite similar to that described in patients with the Klinefelter, Reifenstein, and Albright syndrome. The patient, however, had unilateral cryptorchidism; the pathological changes in the scrotal testis were more marked than those of the cryptorchid testis. In view of this histopathology, had urinary gonadotropins been studied, this might have been the first patient described with hypergonadotropuria.

To conclude this discussion, it is apparent that few patients who have been presumed to have the Laurence-Moon-Biedl syndrome actually have hypogonadism. No patient with classical characteristics of the syndrome, the original pentad described by Laurence and Moon and by Biedl, has been shown to have hypergonadotropuria or hypogonadotropuria. This statement holds for females and for males.

Summary

The Laurence-Moon-Biedl syndrome has become a confused symptom-complex because there has been extreme diagnostic laxity, manifested not only by the failure to include the extraendocrine characteristics described by Laurence and Moon and by Biedl for their patients, but also manifested by a common presumption of the existence of hypogonadism rather than actual proof of its presence. A critical review of the gonadal status of females presumed to have the Laurence-Moon-Biedl syndrome, which included patients reported in the literature, indicates that females with the characteristics of the syndrome, as originally described, are very rare. In none of these has the hypogonadism been qualified as that of congenital aplasia or hypoplasia of the ovaries with hypergonadotropuria or as that due to deficient pituitary stimulation, as manifested by hypogonadotropuria. As a digression, data on males with presumed Laurence-Moon-Biedl syndrome were discussed and the same conclusions were drawn regarding hypogonadism as those drawn for the female. We believe that, in the future, the Laurence-Moon-Biedl syndrome should be diagnosed only when the classical pentad of characteristics, originally described, are present. The hypogonadism of these patients should be real and not presumptive or prognosticated. Furthermore, we urge that the hypogonadism be qualified by studies of urinary gonadotropins, urinary 17-ketosteroids, testicular biopsies, and by other appropriate methods. If this is done, we suggest that the syndrome may be incorporated on the findings of these studies into subgroups of congenital aplasia and hypoplasia of the ovaries or congenital aplasia, hypoplasia, or degeneration of the testes.

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PLASMA ALKALINE PHOSPHATASE

II. Normative Data for Pregnancy

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AS PART of a study of factors affecting the progress of gestation, a series of alkaline phosphatase determinations has been conducted on plasma samples obtained periodically during the antepartum and the postpartum periods. This paper will present the normative data thus obtained. By utilizing a longitudinal method of sampling, evidence was obtained which was of value in interpreting the extent and significance of individual variability. By measuring the degree to which this enzyme is inhibited in the presence of taurocholate, a hypothesis concerning the source of the increased phosphatase during pregnancy is adduced. Certain aspects of dietary and endocrine status are evaluated as possible factors in regulating the activity of plasma alkaline phosphatase.

Although previous investigations¹⁻⁵ have indicated that there is a rise in plasma phosphatase during the last trimester of pregnancy, only two reports^{1, 2} deal with the problem of individual differences. Two studies^{6, 7} were confined to a particular month of pregnancy, three^{2, 3, 5} have dealt in varying degree with the immediate postpartum period, and none have followed up with studies of the infants. The reader is referred to recent reviews^{16, 17} for a more extensive analysis of the literature.

A previous report from this laboratory⁸ deals with the variation and significance of plasma alkaline phosphatase during infancy and childhood.

Method

The analyses reported have been performed on over 400 blood samples obtained from 43 women (55 pregnancies) at monthly intervals during pregnancy and at somewhat longer intervals postnatally. Several of the mothers were studied during repeated pregnancies and information was collected regarding plasma alkaline phosphatase activity in the infants. The subjects selected were mothers enrolled in the research program of the Institute and they were free from any obvious abnormality during and following gestation as judged by routine medical and laboratory examination.

Blood samples were collected, in the presence of heparin, by venipuncture and the plasma analyzed in duplicate samples by the micro procedure of Bessey⁹ under carefully controlled conditions. A model D U Beckman spectrophotometer was used for the measurement of the *p*-nitrophenol liberated from the *p*-nitrophenyl phosphate by the enzyme. The results are expressed in the enzyme units defined by Bessey⁹ and abbreviated here as *NPP units*.

The standard error of duplicate determinations on a random sample of 75 analyses was ± 1.14 per cent, indicating a high precision for the procedure.

Results and Discussion

Normative Values.—

The normative data, together with the statistical evaluation, obtained during this study are presented in Table I, in such a way as to facilitate their clinical use. A total of 51 pregnancies are tabulated. Two cases, to be discussed later, were eliminated from the norms since they were more than 4 standard deviations from the mean.*

The rise in plasma alkaline phosphatase activity, shown graphically in Fig. 1, which starts at the seventh lunar month and continues until delivery, is followed by a rather rapid drop after parturition so that by one month activity is nearly normal. A complete return to normal levels is not evidenced, however, until about the third month post partum.

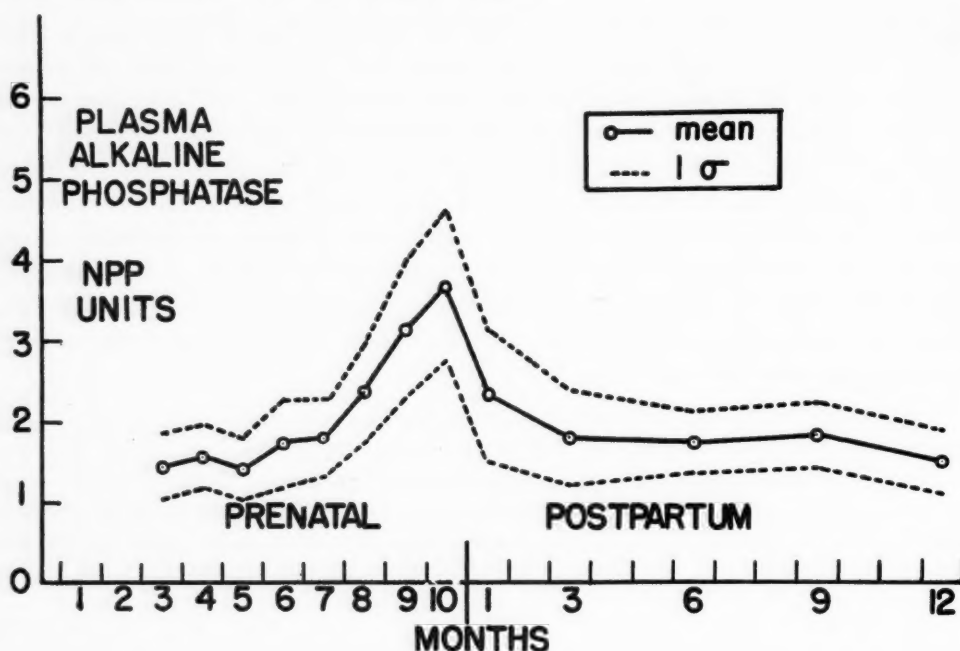


Fig. 1.

Fig. 2 shows the distributions of plasma alkaline phosphatase activity obtained at various lunar months. The tendency appears to be a shift toward the right for the median value after the seventh lunar month with very little "skewing" of the curve until the tenth lunar month. The fact that the distributions tend to remain symmetrical indicates that, generally speaking, the use of standard deviations for comparison of various individuals is justified.

The value of a particular report of normative data depends somewhat upon its relation to the findings obtained in other laboratories. Such a comparison usually cannot be made directly, due to the fact that various chemical methods as well as means of expression of enzyme activity have been used. More recent studies, using more precise methodology, can, however, often be compared by the simple conversion of one system of values to another.

*In such a large number of determinations, inclusion of these cases would have raised the mean only slightly but would have inordinately raised the standard deviation. Whether or not such cases should be excluded may be a matter of debate. However, statisticians are inclined to consider them as "another population" and, practically speaking, because of their disproportionately large effect on the standard deviation and range, they have the effect of hiding deviations which, in most other terms, would be considered significant.

For example, Bodansky¹² units can readily be converted to the nitrophenol phosphate units of Bessey.⁹ Table II shows that a comparison of such converted units reveals a rather surprising concordance. Since it was not possible to convert all of the units to a common basis, the increases found during gestation were calculated. From these calculations it can be seen that all laboratories find that the enzyme activity increases by two to three times during pregnancy, except Meranze,³ who finds a much greater rise. Perhaps the method used by Meranze is more sensitive to the particular alkaline phosphatase(s) that increase during pregnancy; however, this point has not been investigated. The relatively small amount of information concerning the postpartum values will be discussed later. The more general use of the Bessey method, especially when viewed in terms of its close agreement with the findings obtained by the Bodansky method, would seem to be recommended.

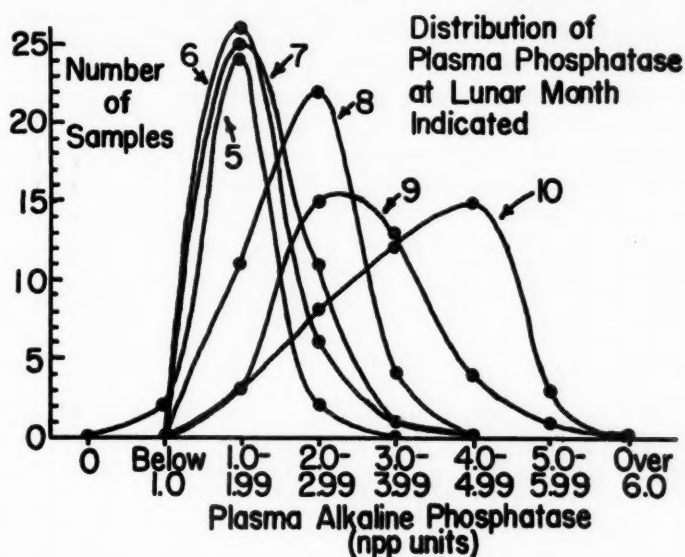


Fig. 2.

TABLE I. PLASMA ALKALINE PHOSPHATASE ACTIVITY IN PREGNANCY

LUNAR MONTH	NO. OF DETERMINATIONS	MEAN	SIGMA*	RANGE
3	6	1.42	0.40	0.91-2.06
4	13	1.51	0.43	0.94-2.55
5	28	1.40	0.38	0.90-2.37
6	33	1.66	0.55	1.00-3.40
7	37	1.76	0.46	1.05-3.12
8	37	2.30	0.61	1.04-3.58
9	36	3.09	0.85	1.47-5.48
10	41	3.67	0.98	1.65-5.75
Total	231	2.31	1.06	0.90-5.75
MONTH POST PARTUM				
1	25	2.31	0.79	1.22-4.78
3	22	1.80	0.55	0.55-3.22
6	22	1.69	0.38	1.07-2.40
9	14	1.78	0.39	1.24-2.56
12	28	1.49	0.38	0.99-2.67
Total	111	1.81	0.62	0.55-4.78

* $\sigma = \sqrt{(1/N) (\sum X^2) - M_{x2}}$

TABLE II. COMPARISON OF VALUES FROM DIFFERENT LABORATORIES FOR PLASMA ALKALINE PHOSPHATASE ACTIVITY DURING PREGNANCY

LABORATORY	REF.	SUBSTRATE USED	N†	LUNAR MONTH OF PREGNANCY											
				3	4	5	6	7	8	9	10	LABOR			
Authors		p-nitrophenyl phosphate	231	1.42	1.51	1.40	1.66	1.76	2.30	3.09	3.67	----			
		% of normal*		----	----	----	117.0	153.0	206.0	245.0	----				
Bodansky	1	β-glycerophosphate	1,053		1.63			1.81	1.99	2.62	3.30	3.69			
		% of normal		----	----			111.0	122.0	161.0	202.0	226.0			
Hoch	5	phenylphosphate	62	1.60	2.04	1.85	1.96	2.26	2.60	4.04		----			
		% of normal		----	----	----	----	122.0	140.0	218.0		----			
Heredia	7	β-glycerophosphate	47									3.96			
		% of normal		----	----	----	----	----	----	----	----	243.0			
Ramsey	6	β-glycerophosphate	97					1.62				----			
		% of normal		----	----	----	----	99.0				----			
Vermehren	2	β-glycerophosphate	134	37.9	42.6	55.5	68.3	63.7	100.7	134.0	143.0	152.0			
		% of normal		----	----	----	----	124.0	197.0	262.0	280.0	297.0			
Meranze	3	β-glycerophosphate	293		2.08	2.45	3.02	3.36	4.79	8.33	10.35	12.53			
		% of normal		----	----	----	----	133.0	190.0	331.0	411.0	499.0			
Kerleau	4	β-glycerophosphate	46		17.1			13.8	25.3	21.1	31.3	----			
		% of normal		----	----	----	----	81.0	148.0	123.0	183.0	----			

*Per cent of normal has been calculated by using the average value for the 3-6 lunar month as a base line whenever these data were available. A normal value of 1.63 as given by Bodansky† was assumed in calculating the results of Heredia and of Ramsey since they did not report normal values for women. Some retabulations, from raw data, were made in certain instances.¹⁻³

†Bodansky units have been converted to NPP units by multiplying by the factor 0.56 as reported by Bessey,³ and King-Armstrong units to NPP units by multiplying by 0.28 since Greenberg² reported that King-Armstrong are about twice Bodansky units.

‡N = total number of samples analyzed for antepartum periods shown in table.

Individual Cases.—

An inspection of Fig. 3, in which various individual cases have been plotted, reveals several interesting facts. First, some cases, such as DU-11, show relatively little increase during pregnancy while others, such as ES-21, show sizeable increases during normal pregnancies.

Second, occasional cases, such as CV-211 and GN-11, exhibit such remarkable increases that they must be regarded as unique and cannot be justifiably included in the statistically derived norms. A similar phenomenal rise in an otherwise normal pregnancy has been reported by Bodansky.¹ These cases deserve some comment.

Case CV-211 had normal serum calcium levels¹⁴ during her third pregnancy and normal serum calcium and inorganic phosphate¹⁵ values during her fourth pregnancy in spite of the elevated phosphatase. Her diet-record analyses revealed no deficiencies and she was taking a daily supplement of 1,000 I.U. of vitamin D during her third, and 500 I.U. during her fourth pregnancy. Aside from the fact that her second (not studied) and her fourth child had clubfoot, no abnormal findings were evident in the medical history. Perhaps congenital clubfoot is somehow related to a characteristic, possibly genetically determined, elevation of plasma alkaline phosphatase.

The second case, GN-11, showing an abnormally elevated plasma phosphatase also exhibited no clinical evidence of abnormality during this pregnancy. Her diet could certainly be classified as adequate although she was taking no supplements of any kind. Whether Dilantin therapy, instituted during a previous pregnancy when epilepsy-like seizures (first reported at the age of 16 years) began, had any influence on the phosphatase level must remain obscure for the present. The infant was perfectly normal and healthy at birth.

A third point, with regard to individual cases, is that it is quite apparent that a given mother very definitely reveals a characteristic pattern during repeated pregnancies. In case ES-21, the similarity in the values is striking, but even the special case just described, that of CV-211, can also be said to show a characteristic phosphatase response to pregnancy. Such data, of course, emphasize the fact that genetic factors probably play a major role in determining the level of plasma alkaline phosphatase activity.

Exogenous Factors.—

As part of the approach to the understanding of the significance of the changes of plasma phosphatase during pregnancy various possible areas of variation were analyzed.

Of the 22 women on whom one month post partum plasma phosphatase analyses were made, 11 were nursing their infants at this time. The mean value for the lactating women was 2.25 and the mean for the nonlactating was 2.52, the difference being not significant ($P = 0.45$), using Fisher's "t" analysis.²¹ The fact that these women had values which were not significantly different ($P = 0.6$) at the fifth month of pregnancy indicates that chance selection factors did not obscure any real differences. These data are not in accord with the conclusions of Vermehren,² who stated that during lactation the plasma phosphatase is moderately elevated while in nonlactating women the phosphatase is back to prepregnancy values about four weeks after delivery. It should be noted, however, that Vermehren has but little data at four weeks post partum and has not subjected it to statistical analysis. A recent report²⁰ concludes that the puerperal level of phosphatase activity remains slightly higher in women who are lactating. However, recalculation of their raw data indicates a mean of 3.10 for nonlactating women, instead of the value of 2.93

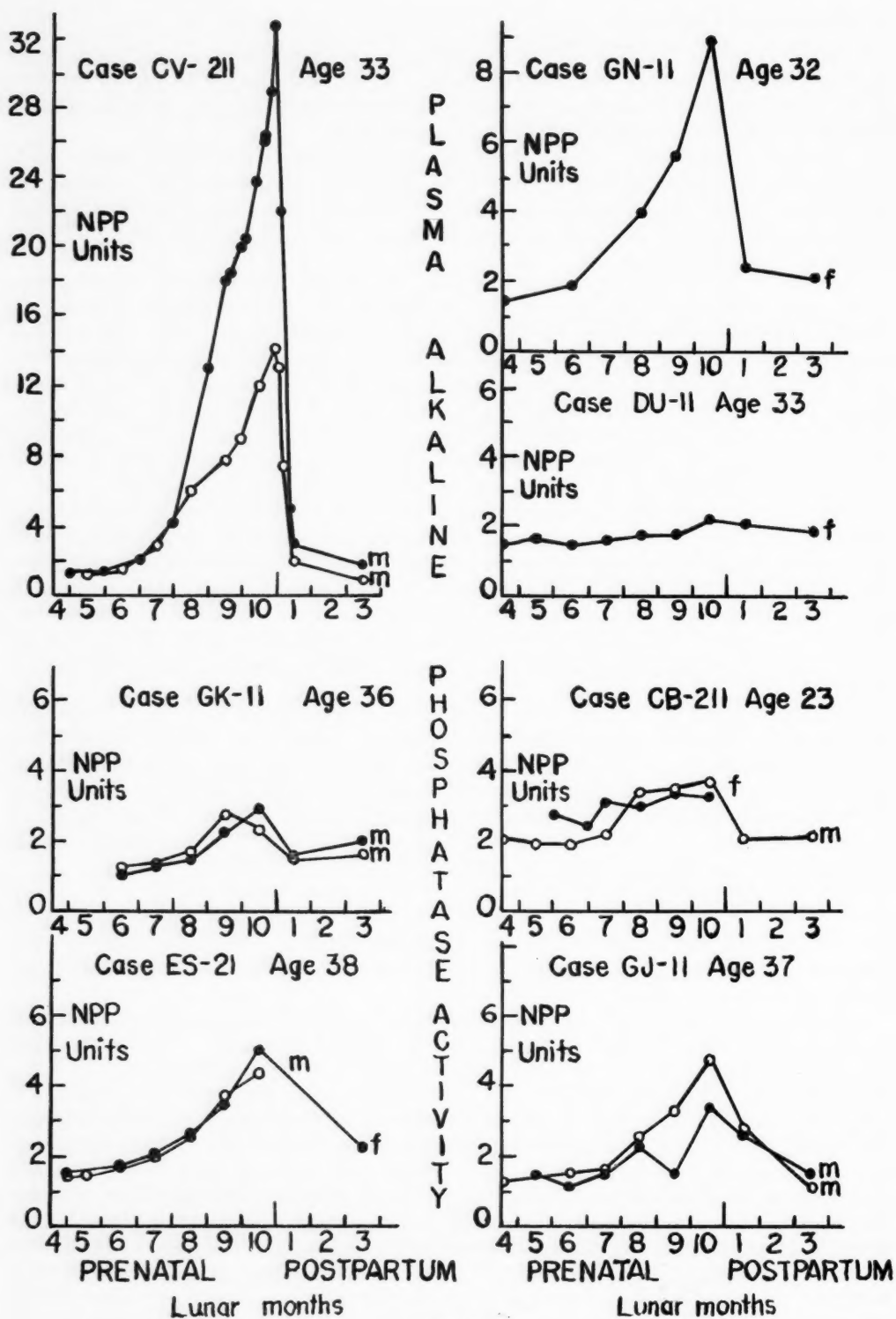


Fig. 3.

given, and statistical evaluation of the results indicates that the difference cannot be considered significant ($P = 0.15$).

For purposes of searching for possible relationships between plasma alkaline phosphatase and diet, the mothers were divided into three groups on the basis of the enzyme activity in the tenth lunar month. The highest 15 had a mean value of 4.75; the middle 13, 3.78; and the lowest 15, 2.58. The search, on this basis, revealed no significant relationships for the following items: vitamin D supplemented vs. nonsupplemented; vitamin C supplemented vs. nonsupplemented; thiamine, riboflavin, and niacin status as judged by load tests; plasma vitamin A and carotene; plasma protein, hemoglobin, and red-cell count.

Our data give equivocal results when analyzed for seasonal effects. Antepartum plasmas show a higher activity in June through August ($M = 2.18$) than in October through December ($M = 1.84$), a difference which can be regarded as bordering on significance ($P = .066$) with suitable corrections for sex of the fetus and period of gestation. However, a similar analysis of postpartum plasmas does not reveal a significant shift dependent on season.

Endogenous Factors.—

Apparently the age of the mother is not related to the extent of the rise in plasma alkaline phosphatase during pregnancy since the 10 oldest mothers ($M = 39.8$ years) had a mean value of 3.50 units, while the 10 youngest mothers ($M = 23.2$ years) had a mean value of 3.44 units. Similarly, the average age of the 15 mothers having the highest phosphatase values was 33.9 years, while that of the lowest 15 was 33.3 years.

The 12 women who had had one or more spontaneous abortions or miscarriages had a mean plasma phosphatase activity of 3.75 units which did not differ significantly ($M = 3.66$) from that of 30 women who had no history of abortions. Table III indicates a tendency for the tenth lunar month plasma alkaline phosphatase to be greater in women who have had several pregnancies than in those who have had only one. The difference, however, only becomes highly significant when primiparas are compared with those who have had five or more pregnancies. Unfortunately, the number of cases available for this comparison is small enough for the difference to be regarded with skepticism.

TABLE III. RELATION BETWEEN THE NUMBER OF PREGNANCIES AND THE 10 LUNAR MONTH PLASMA ALKALINE PHOSPHATASE

	SEX OF FETUS	N	MEAN NPP UNITS	SIGMA	P
1 pregnancy	M	4	3.72	0.17	0.45
2-4 pregnancies	M	16	4.06	0.91	
1 pregnancy	F	5	2.90	0.56	0.65
2-4 pregnancies	F	8	3.14	1.10	
1 pregnancy	M	4	3.72	0.17	>0.01
5-7 pregnancies	M	4	4.40	0.23	

The data in Table IV reveal that by the tenth lunar month of pregnancy there is a highly significant difference between the plasma alkaline phosphatase activity of women bearing male fetuses and those bearing female. That this effect is not due to some chance selection factor is shown by the fact that there is no difference between the plasma of the groups when postpartum samples are analyzed. Although there is a difference between the weights of males and females at birth in these groups, as would be expected, it is difficult to see how this can explain the phosphatase difference. One might expect, in terms of

findings described below, that differences in placental weight might be involved. A recent report¹⁸ indicates a relationship between placental weight and birth weight. Placental weights for the pregnancies in Table IV were not available. Perhaps the effect is related to hormone elaboration by the fetus. But, whatever the cause, it is apparent that fetal sex must be taken into consideration, as it has been here, in comparisons of various groups of women in terms of plasma alkaline phosphatase.

TABLE IV. SEX OF FETUS

LUNAR MONTH	SEX OF FETUS	N	PLASMA ALKALINE PHOSPHATASE NPP UNITS	P	INFANT WEIGHT KG.
7	M	20	1.85	0.20	
	F	11	1.59		
8	M	18	2.33	0.53	
	F	11	2.18		
9	M	19	3.21	0.18	
	F	10	2.75		
10	M	20	4.13	0.01	3.405
	F	11	3.23		3.172
Post partum					
1	M	16	2.28	0.70	
	F	5	2.45		

Comparison of the high, middle, and low tenth lunar month phosphatase activities, interestingly, revealed no significant differences in hemoglobin and red-cell count, as mentioned before, and in white-cell count, differential-white-cell count, blood sugar, excretion of creatine, basal metabolic rate, and 17-ketosteroid excretion.

Source of Plasma Phosphatase.—

Bodansky's studies,¹⁰ confirmed by Gould,¹¹ revealed that phosphatase derived from intestinal tissue is not inhibited by sodium taurocholate (0.00625M) while that from kidney and bone is. It was later found⁸ that the phosphatase activity of placental extracts was not inhibited by taurocholate while that circulating in the plasma of growing children was inhibited about the same amount as that derived from bone and kidney. Table V reveals that the taurocholate inhibition of pregnancy plasma phosphatase decreases during gestation. If one calculates the *absolute* activity which is inhibited by taurocholate, a constant value is obtained. In the case of CV-211 (Fig. 3), the plasma alkaline phosphatase from the seventh to the tenth lunar months showed 100 per cent activity in the presence of taurocholate, remained this high in a sample taken at the first day post partum, and then dropped to 59 per cent by the fourth week. Cord blood from this case showed 58 per cent activity. Similar results were obtained using the plasma of Case GN-11.

These findings strongly suggest that the plasma alkaline phosphatase which increases during the last trimester of pregnancy is derived mainly, if not entirely, from the placenta. It is suggested that taurocholate inhibition of pregnancy plasma samples may provide a means of differentiating placentally derived enzyme from other types which may be conceived as existing in certain disorders of pregnancy.

Although the placental phosphatases have been subjected to histological examination,¹⁹ the origin in the placenta of that found in the plasma is not yet certain.

Relation to Infant Status.—

That the plasma alkaline phosphatase does not pass the placental membrane is revealed by the fact that the plasma phosphatase value of the cord blood in Case CV-211 was only 4.82 units and the infant at 1 day had a value of 6.38 units. Furthermore, the infants between 1 and 3 months from the 9 highest maternal tenth-lunar month values had a mean value of 8.47, while those from the lowest 9 had an activity of 8.26 units. This concurs with the recent conclusions of Speert.²⁰

The infants who nursed had a mean phosphatase value of 8.10 units, while those fed by formula had a value of 9.42 units. The difference, indicating a trend toward higher enzyme activity in the artificially fed infants, cannot be regarded as significant ($P = 0.25$).

TABLE V. RELATIVE ACTIVITY OF PLASMA ALKALINE PHOSPHATASE IN THE PRESENCE OF TAUROCHOLATE

LUNAR MONTH	N	MEAN PHOSPHATASE ACTIVITY			RELATIVE ACTIVITY IN PRESENCE OF TAUROCHOLATE %
		TAUROCHOLATE ABSENT NPP UNITS	TAUROCHOLATE PRESENT NPP UNITS	DIFFERENCE NPP UNITS	
5	4	1.37	0.73	0.64	53
6	4	1.48	0.96	0.52	65
7	5	1.93	1.29	0.64	67
8	5	2.06	1.46	0.60	71
9	6	3.27	2.85	0.42	87
10	8	3.62	3.02	0.60	83
POST PARTUM					
1	6	2.05	1.35	0.70	66
3	8	1.65	0.94	0.71	57
6	5	1.46	0.81	0.65	56
9-12	3	1.73	0.94	0.79	54

Summary

1. To provide normative data for plasma alkaline phosphatase in uncomplicated pregnancies, over 400 plasma samples were analyzed by the micro method of Bessey and Lowry.

2. Occasional cases deviate widely from the general population for no apparent reason.

3. Plasma alkaline phosphatase values tend to follow a pattern which is characteristic for a given individual as determined by studies of repeated pregnancies.

4. Lactation does not significantly alter the plasma alkaline phosphatase level.

5. There was no discernible relation between the plasma alkaline phosphatase activity and dietary factors or hematological measurements.

6. Equivocal results were obtained with respect to seasonal variations.

7. Women bearing male fetuses, on the average, have higher plasma phosphatase values than those bearing females. This factor must be taken into account in statistical calculations involving other variables.

8. The increased plasma alkaline phosphatase may be derived from the placenta as judged by taurocholate inhibition studies.

9. It can be concluded that there is a 200 to 300 per cent increase of plasma alkaline phosphatase in the last trimester of pregnancy, as judged by the general concordance of data reported by various laboratories.

10. The alkaline phosphatase activity of the maternal plasma bears no relation to that of the cord blood or of the infant at birth.

The authors wish to thank Dr. L. W. Sontag for valuable suggestions and criticisms during the course of this investigation and to acknowledge the technical assistance of Miss Elizabeth Snook and Miss Mary Davis. We are indebted to Dr. Renée Portray for the serum calcium determinations.

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FACTORS INFLUENCING THE URINARY EXCRETION OF CALCIUM*

II. Pregnancy and Lactation

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IN THE first paper of this series¹ the factors influencing the excretion of calcium in the urine of normal persons were discussed, and the normal range of urinary excretion of calcium was established. It was found that the quantity of urine calcium is dependent on an endogenous (probably endocrine) factor or factors and on calcium intake per units of weight. Age and sex were not factors except as they affect weight, and, with the exception of acid, dietary factors other than calcium intake have relatively minor effects. Thus it was possible to compare data from subjects of all ages and with varying dietary intakes. Urinary calcium expressed as per cent of calcium intake was found to vary inversely with the calcium intake per kilogram and to be an exponential function of the latter. Values for mean, minimum, and maximum normal urinary calcium can be expressed by specific equations. This new tool promised to be of considerable aid in further studies of calcium metabolism in various conditions.

In studies of pregnant women carried out in this laboratory² it was noted that the urinary calcium excretion often was much higher than that of a group of nonpregnant women of the same age and similar dietary regimen. Shortly before or immediately after parturition the urinary calcium decreased sharply. These observations were difficult to evaluate, because the normal range of urine calcium was not known, and because the influence of other factors, such as the change in weight of the individual, on urinary calcium could not then be determined. With our present knowledge of the range of urinary calcium excretion in normal persons, it seemed pertinent to re-examine the data on urinary excretion of calcium by pregnant and lactating women.

Pregnancy

The data used for this study were compiled from 56 five- or seven-day studies of 7 pregnant women made in this laboratory and 255 studies of 82 women reported by others.³⁻¹⁵ A summary of the calcium data for the subjects studied in this laboratory is given in Table I. The women's ages varied from 14 to 30 years. One subject was studied during three successive pregnancies, two subjects had been studied previous to the pregnancy, and postpartum studies were obtained on 2 subjects. Table II shows the average urinary calcium and

*The greater part of this paper is taken from a dissertation submitted by Elizabeth L. Knapp in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in the Department of Chemistry in the Graduate College of the State University of Iowa.

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TABLE I. URINARY EXCRETION OF CALCIUM BY PREGNANT WOMEN

SUBJECT	AGE IN YEARS	WEEK OF PREGNANCY	WEIGHT IN KG.	CALCIUM INTAKE		RETENTION GM./DAY	URINE CALCIUM		
				GM./DAY	MG./KG.		MG./DAY	PER CENT OF INTAKE	
R. C.	13	*	45.8	1.353	30	0.367	163	12.0	
	14	30	51.6	1.360	26	0.231	363	26.7	
		31	52.1	1.362	26	0.363	258	18.9	
		32	52.8	1.646	31	0.466	232	14.1	
		33	52.9	1.666	31.4	0.360	259	15.3	
		34	54	1.771	33	0.544	259	14.6	
		35	55.2	1.661	30	0.493	231	13.9	
		36	55.4	1.761	32	0.216	298	16.9	
		37	56.7	1.998	36	0.486	302	15.1	
		38		2.049	35.5	0.673	336	16.4	
		39	57.8	2.130	37	0.625	263	12.3	
		**	51.7	1.938	37.5	0.156	147	7.6	
	F. B.	23	34	57.5	1.843	32	0.488	311	16.9
			36	58.7	1.708	29	0.262	277	16.2
		37	58.7	1.708	29	0.377	254	14.9	
J. G.		21	57.3	1.950	34	0.039	387	19.8	
		24		2.023	35	0.010	357	17.3	
		27	61.3	1.964	32	0.008	361	18.4	
		32	63.2	2.114	33	0.249	333	15.8	
		34	64.5	2.087	32	0.451	308	14.8	
		36		2.102	33	0.280	290	13.8	
V. V.		22	60.5	2.037	34	0.165	220	10.8	
		23		2.403	38	0.090	252	10.9	
		25	62.0	2.035	33	0.402	231	11.4	
		30		1.906	30	0.244	389	20.4	
		34	65.0	2.180	34	0.222	571	25.0	
		37	66.0	1.693	30	0.139	415	24.5	
	R. I.	29	13		1.860		0.449	390	21.0
		18		1.791		0.294	281	15.7	
		21		1.717		0.064	223	13.0	
		***	59	2.119	36		197	9.3	
M. O.	22	25	54	1.362	25	-0.115	214	15.7	
	26	29	63	1.753	28	0.050	323	18.4	
		32	63.7	1.799	28	0.230	264	14.7	
		35	65.5	1.922	29.5	0.128	314	16.3	
	M. O.	29	1	57	1.083	18.5	0.097	111	10.3
		6	56	1.062	19	0.068	154	14.5	
		9	55	1.158	21	0.055	152	13.7	
		12	56	1.540	27.5	0.223	157	10.2	
		18	57	1.632	28.6	0.122	302	18.5	
		4	57.5	1.145	20	-0.177	133	11.6	
M. O.	30	10	58	1.727	30	0.072	231	13.4	
		11	57.7	1.832	31.5	0.082	258	14.1	
		13		1.730		0.017	337	19.5	
		14		1.772		0.113	345	19.4	
		18		1.753		0.268	338	19.3	
		19		1.689		0.057	327	19.4	
		23		1.586		0.280	408	25.8	
		24		1.833		0.068	502	27.6	
		28		1.906		0.172	315	16.5	
		29		1.887		0.461	296	15.7	
		32	69.0	1.868	27	0.636	322	17.2	
		33		1.945		0.235	320	16.5	
		35		1.961		0.451	292	14.9	
		36		1.867		0.470	280	15.0	
	E. W.	30	24		1.803		0.244	254	14.1
		29		1.695		0.111	224	13.2	
		35		1.684		0.450	292	17.3	
		39	62.2	1.664	27	0.132	263	15.8	
		****	62.3	1.532	25	0.307	70	4.6	

*Nonpregnant. This period of study occurred one year previous to present series.

**Two weeks post partum.

***Nonpregnant.

****Nine weeks post partum.

the range of observed values for each week of pregnancy for all studies of pregnant women receiving more than 0.8 Gm. of dietary calcium daily. It is obvious that the maximum values for urinary calcium are unusually high during the entire last half of pregnancy.

TABLE II. MEAN AND RANGE OF VALUES FOR URINARY CALCIUM EXCRETION OF PREGNANT WOMEN, AS RELATED TO WEEK OF PREGNANCY*

WEEK OF PREGNANCY	NO. OF PERIODS	URINE CALCIUM	
		MEAN	RANGE
		MG./DAY	
1	1	111	
2	1	43	
3	0		
4	1	133	
5	0		
6	2	199	154-244
7	0		
8	3	249	120-328
9	3	200	158-256
10	2	255	
11	2	267	
12	6	197	121-271
13	6	299	241-390
14	3	389	298-524
15	1	473	
16	5	270	186-310
17	5	227	175-291
18	6	260	111-338
19	2	287	246-327
20	6	260	123-420
21	9	277	183-387
22	5	269	195-326
23	5	257	137-408
24	7	257	137-502
25	5	284	214-445
26	6	306	124-500
27	6	247	82-413
28	12	254	135-380
29	9	308	152-490
30	17	309	121-697
31	8	305	60-594
32	16	285	111-495
33	13	268	103-509
34	34	285	57-635
35	10	320	168-557
36	20	297	41-533
37	10	240	67-415
38	16	278	76-669
39	14	241	99-545
40	6	210	35-482

*Values from author's data and the literature.³⁻¹⁵

The $\frac{\text{urine Ca} \times 100}{\text{intake Ca}}$ was plotted against calcium intake per kilogram for the 16 subjects for whom sufficient data were obtainable (Fig. 1). The curves for maximum, mean, and minimum normal values are shown in the same figure. The distribution of values shows a definite tendency toward increase in urine calcium above the normal mean during pregnancy. Nearly half of the maximum values are at or above the normal maximum.

The changes in urinary calcium excretion with progression of pregnancy are illustrated in Figs. 2, 3, and 4. The data used are from the literature and

our own subjects; the curves are representative of the findings for all subjects. Urinary calcium tends to increase to a maximum, which occurs some time after the twentieth week and in a few subjects is not reached until term. The decrease in urine calcium excretion observed in most subjects toward the end of pregnancy demonstrates that previous increases were not related primarily to changes in body weight. The effect of various dietary components other than calcium on the calcium metabolism in these subjects appeared to be negligible.^{4, 15}

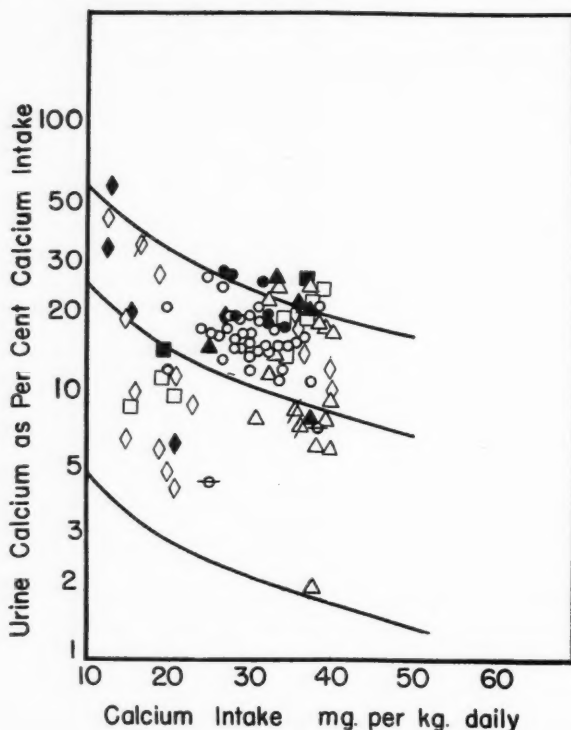


Fig. 1.—The excretion of calcium in urine during pregnancy. The background lines represent the maximum, mean, and minimum normal values for urinary calcium, expressed as per cent of intake, in relation to the intake of calcium per kilogram daily. The maximum value for each subject is shown as a solid symbol. Symbols with cross lines indicate values obtained from the given subject during nonpregnant periods. To allow sufficient spread of intake levels, arithmetic scale is used for the abscissa.

After parturition and seemingly independent of lactation, the urinary calcium is greatly reduced from antepartum levels. The amount of calcium excreted in the urine may decrease from values as high as 600 mg. to less than 100 mg. daily in the first few weeks after parturition, even though the calcium intake be maintained constant or even increased. The amount of decrease in urine calcium is apparently independent of the level of excretion antepartum (Figs. 2 and 4).

The only reported study wherein a normal pregnant woman received a diet very low in calcium is that of Bauer and collaborators.¹⁶ This subject ingested a diet containing approximately 100 mg. of calcium daily (as read from chart) and excreted 100 per cent of the intake in each of the 3 studies made during the fifth and eighth months of pregnancy and six weeks after delivery by cesarean section. The constancy of these values in contrast to the rise and later fall usually observed suggests a minimum level of excretion by the kidney under the given conditions.

Lactation

The data on 43 studies of calcium metabolism of 15 lactating women reported by others^{14, 15, 17} together with 33 studies of women collected in this laboratory have been used for this analysis. The data for the studies made in this laboratory are given in Table III.

In general the urinary calcium excretion during early lactation is much lower than during pregnancy, although the intake of calcium is usually greater during lactation.^{14, 15} The level of urinary excretion is, in fact, often lower than expected for nonpregnant women receiving similar very high calcium intakes. With continuation of lactation the urinary calcium excretion tends to increase, although the calcium intake may be constant and adequate milk flow is maintained. These changes in urinary calcium are illustrated in Figs. 2, 3, and 4.

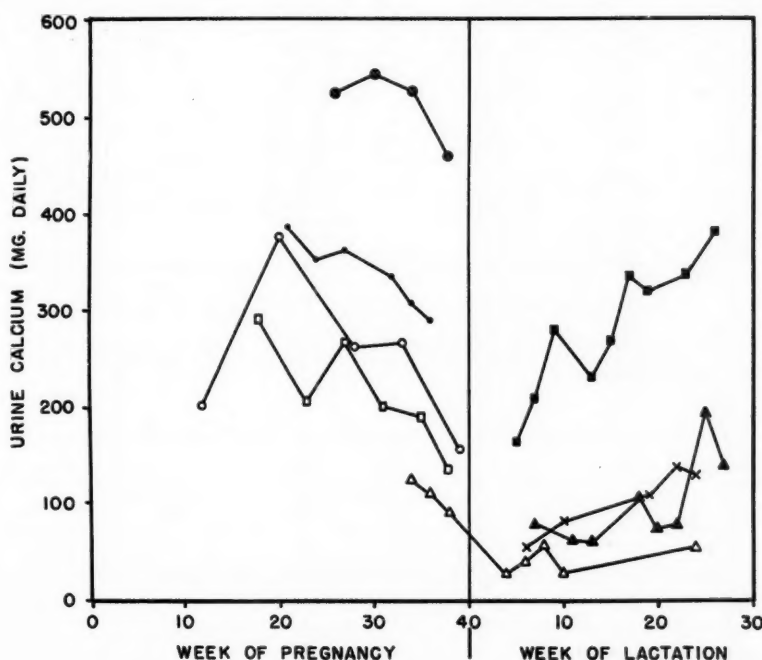


Fig. 2.—The excretion of calcium in urine during pregnancy and lactation. Each curve depicts data from one subject. These subjects showed a tendency toward maximum excretion about the twentieth week of pregnancy, and a tendency toward increasing urinary excretion with duration of lactation.

The effect of unusually long and heavy lactation was studied by Hunscher, Donelson, and others^{17, 18} in 3 subjects whom Macy¹¹ had studied during the pregnancies just preceding. All the subjects secreted large quantities of milk for periods of 40 to 60 weeks. The urinary calcium values for 2 of these subjects were found to decrease sharply from 669 and 494 mg. daily, respectively, in late pregnancy, to 70 and 71 mg., respectively, in the seventh week of lactation. By the sixty-second and sixty-third weeks of lactation all 3 subjects showed enormously high urinary calcium levels of 1.23, 1.36, and 2.05 Gm. daily. These are the highest values for excretion of calcium in the urine reported for supposedly normal individuals. During a postlactation period of reproductive rest in 2 of these subjects, the urinary calcium remained as high as 1.82 and 1.01 Gm. daily at 11 and 13 weeks, respectively. At 41 and 45 weeks after lactation, the urinary calcium had declined to levels of 410 and 230 mg.,

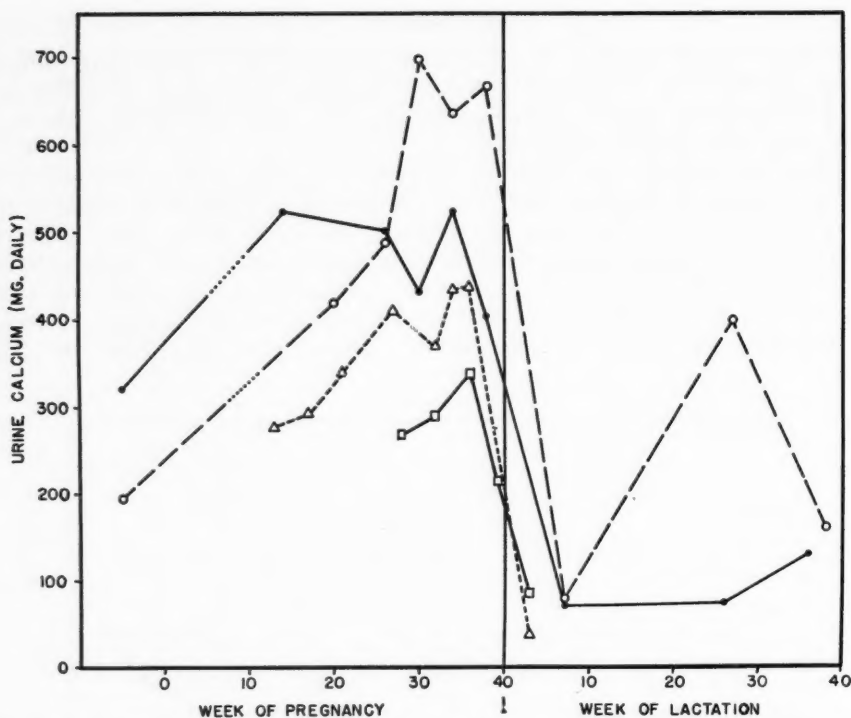


Fig. 3.—The excretion of calcium in urine during pregnancy and lactation. These 4 subjects attained maximum excretion near the thirtieth week of pregnancy, with a marked postpartum decrease in excretion.

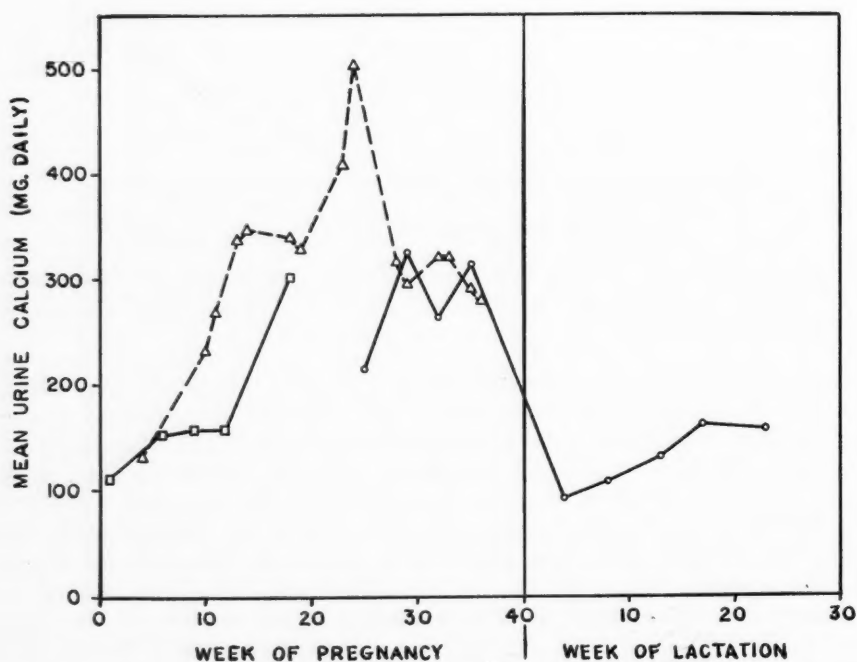


Fig. 4.—The excretion of calcium in urine during pregnancy and lactation. These curves show data obtained from one subject during 3 successive pregnancies and one lactation. The second pregnancy was terminated at the fifth month.

TABLE III. URINARY EXCRETION OF CALCIUM BY LACTATING WOMEN

SUBJECT	WEEK POST PARTUM	WEIGHT IN KG.	CA INTAKE		CALCIUM RETENTION MILK		URINE CALCIUM	
							MG./DAY	PER CENT OF INTAKE
H. L.	5	59.5	1.557	31.2	-0.271	0.178	165	10.6
	7		2.792	46.9	0.602	0.198	208	7.4
	9		2.850	47.4	-0.833	0.267	281	9.8
	11		2.990		0.383	0.250	282	9.4
	13		2.789		0.715	0.294	230	8.3
	15		2.783		0.481	0.293	269	9.6
	17		2.675		0.811	0.257	333	12.5
	19		2.817		0.159	0.365	321	11.4
	23		2.912		0.437	0.272	338	11.6
	26		2.913	52	0.245	0.169	381	13.1
	26	56.3	2.913	52	0.245	0.169	381	13.1
E. P.	7	47.8	3.024	63.5	0.179	0.156	78	2.6
	11		2.571	53.6	0.091	0.318	63	2.5
	13		2.965		0.866	0.240	61	2.1
	18		2.545		-0.265	0.244	106	4.0
	20		2.560		0.004	0.231	75	2.9
	22		3.130		0.343	0.238	79	2.5
	25		3.130	67.5	0.417	0.053	195	6.2
	27		1.400	30.3	0.274		140	10.0
E. S.	6	66.6	2.101	31.6	-0.492	0.218	53	2.5
	10		2.173		0.063	0.572	81	3.7
	19		2.342		0.121	0.332	109	4.6
	22		2.342	36.8	0.117	0.272	139	5.9
	24		1.766	27.4	0.903		128	7.2
B. J.	12	60	1.450	29	0.207	0.183	54	3.7
	16		1.597	31.8	0.003	0.123	86	5.4
	22		1.346		-0.198	0.108	72	5.4
M. O.	4	60	2.055	34.4	-0.231	0.130	92	4.5
	8		2.021	34	-0.569	0.168	108	5.3
	13		2.047		-0.198		131	6.2
	17		2.571	44.5	-0.081	0.151	164	6.3
	23		2.860	49	0.281		159	5.6
R. C.	2	51.7	1.938	37.5	0.156		147	7.6
E. W.	9	62.3	1.532	25.0	0.307	0.090	70	4.6

respectively, values which are within normal range for the intakes. Both these women were losing large amounts of calcium from the body, particularly in the late lactation and postlactation periods. It is difficult to explain the large losses of calcium which occurred 10 months after the cessation of lactation, when it was assumed that the maternal organism would have recovered from the severe strain of several cycles of pregnancy and milk secretion repeated in rapid succession.

The lactation data were recalculated as $\frac{\text{urine Ca} \times 100}{\text{intake Ca}}$ and plotted

against intake per kilogram, as was done for the data from pregnancy. The results are shown in Fig. 5. Distinction has been made between studies of lactation periods under 10 months' duration and those of more than 10 months. For lactation periods of customary length, urine calcium excretion values tended to be below the mean observed for normal individuals and considerably lower than the mean value observed for the pregnant women (Fig. 1).

Fig. 5 illustrates also the marked increase in urinary calcium excreted by the women with lactation periods of excessive length.¹⁸ The values for 2 of the 3 women were well above the normal level and remained abnormal for 3 months after cessation of lactation. Ten months post lactation, the urinary calcium values for both women were within the normal range (slashed figures).

Reviewing the whole reproductive cycle of pregnancy and lactation from the data which we have gathered, the urinary calcium seems to vary in cyclic fashion, showing an increase above normal in the latter half of pregnancy, a sharp decrease at parturition and during early lactation, an increase above normal levels if lactation is prolonged, and a slow decrease to normal levels during reproductive rest.

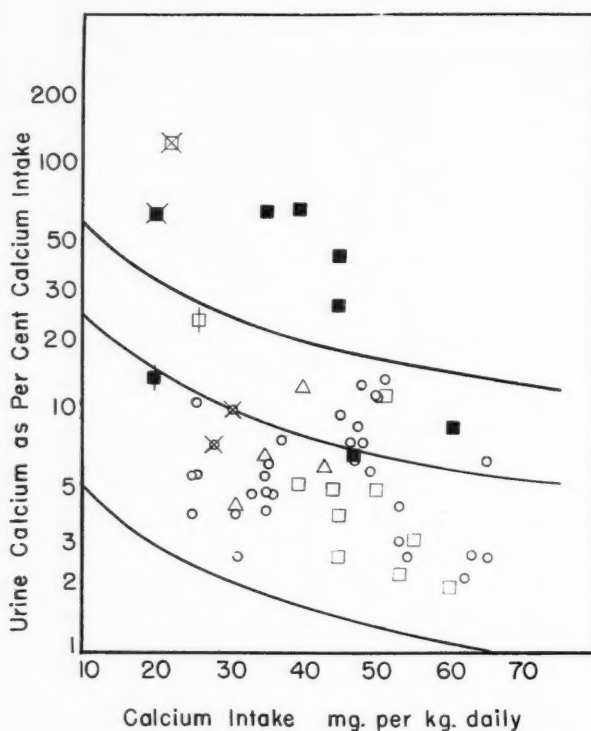


Fig. 5.—The urinary excretion of calcium during lactation. Data for lactation periods of less than 10 months' duration are reported as hollow symbols; studies after the fortieth week of lactation are shown as solid symbols. Studies from 1 to 13 weeks post lactation are shown by crossbars through the given symbol. Two of the 3 women with lactation periods of excessive length were studied at 11 and 41 weeks and 13 and 45 weeks post lactation, respectively. The perpendicular line through the symbol indicates periods more than 10 weeks after the end of the lactation period. To distinguish between subjects, the postlactation symbols for one subject are left hollow, though lactation lasted more than 60 weeks.

Other Studies of Female Sex Hormones

The role of the female sex hormones in regulating the "normal" level of urinary calcium for the individual, perhaps as a part of the "endogenous factor,"¹ has not been determined, nor is it known which hormones are responsible for the changes in urinary calcium in pregnancy and lactation.

Recently a 2½-year-old girl with precocious puberty was studied in this clinic. The child had menstruated since the age of 5 months and was large for her age, with mammary development and pubic hair. She excreted 98 mg. of calcium in the urine daily which was 47 per cent of her calcium intake of 208 mg., or 14 mg. per kilogram. This excretion is just above the normal maximum. The estrogen titer of the urine was 65 rat units per day* (a value of the order found in an adult who is 8 weeks pregnant). Air encephalograms gave no evidence of tumor of the third ventricle; abdominal exploration showed greatly enlarged ovaries, one of which contained a yellowish mass. The enlarged ovary

*We are indebted to Dr. Emil Witschi of the Department of Zoology for this figure.

was removed and sectioned for study. It proved to be a normal mature ovary with a normal corpus luteum. The lack of agreement in the degree of elevation of urinary calcium and estrogen levels would suggest a lack of importance of estrogens in influencing urinary calcium excretion.

Johnston¹⁹ has reported serial studies of calcium metabolism of girls at puberty. Six-day average values for urinary calcium showed no evidence of consistent cyclic changes in urinary calcium occurring in relation to the menstrual cycle. Johnston²⁰ also gave 2,000 units of estrone daily to normal girls at puberty. The calcium retention was depressed in 5 of the 6 subjects, but no consistent effect of the hormone on urinary calcium could be observed.

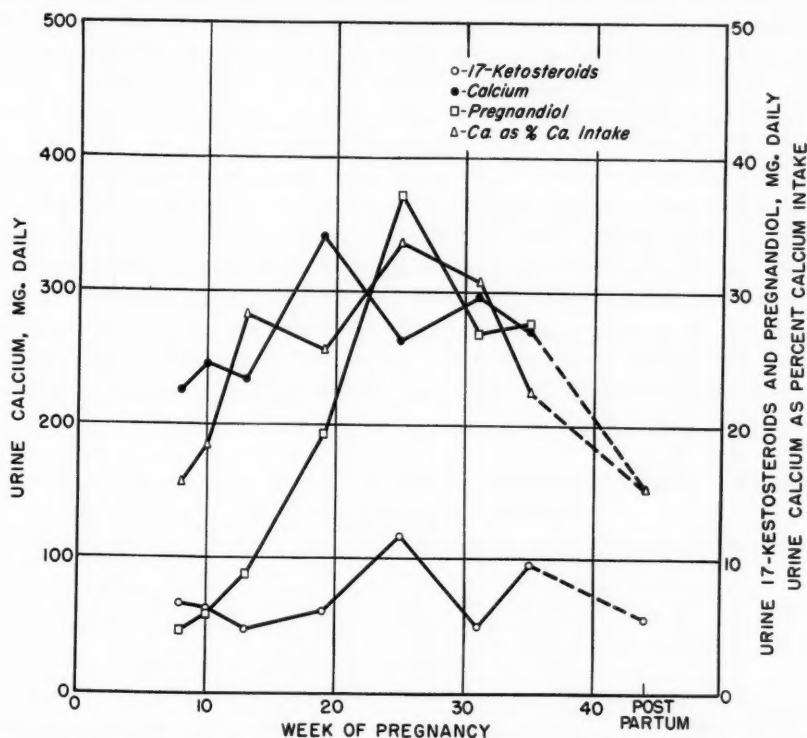


Fig. 6.—The excretion of calcium, 17-ketosteroids, and pregnandiol in urine by one young woman during pregnancy. These data suggest a possible relationship between the factors regulating the urinary excretion of pregnandiol and calcium.

The findings discussed above suggest that for the woman who is neither pregnant nor lactating the sex hormones are a relatively minor factor in determining the amount of urine calcium. During pregnancy, however, the picture is less clear. Not only are the amounts of estrogens, pregnandiol, and gonadotropic hormone in the urine greatly increased,²¹ but hyperplasia of the parathyroids has been demonstrated in pregnant animals.²² Also, a recent study of adrenal function in human pregnancy may indicate a possible relationship of the adrenal cortex to urinary calcium excretion. Venning²³ found a sharp rise in urinary excretion of glyconic corticoids which reached a peak at about 100 days and returned to normal by 120 days ante partum. Later, a second rise in corticoids to much higher levels occurred, which increase reached a peak at about 240 days. Usually corticoid excretion decreased during the last month of pregnancy and always dropped sharply to normal levels after parturition. The similarity of the curve for corticoid excretion, especially during the second rise, and the curve for urinary calcium excretion is suggestive of a possible relation-

ship between the two. Venning also noted a steady increase in the ketosteroid excretion, attributed to the 20-ketosteroids or pregnanolones, which reached a maximum just before parturition and returned to normal after parturition. The maximum excretion of estrogens and pregnandiol also is reached just before parturition.²³

In an attempt to investigate the possibility of a relationship between the female sex hormones and the excretion of calcium in the urine, we have studied the urinary excretion of calcium, 17-ketosteroids, and pregnandiol during pregnancy in one young woman. The subject was a Chinese woman, 27 years old, who was studied at approximately monthly intervals from the second month of her second pregnancy to term, and one month post partum. Urine was collected daily for 4 or 5 days, and a careful record kept of the food eaten during those five days. The calcium intake was calculated from standard tables of food composition and the urine was analyzed for calcium and phosphorus, creatine and creatinine, 17-ketosteroids²⁴ and pregnandiol.²⁵ Chemical determinations of estrogens and 11-oxysteroids (corticoids) were attempted but were unsuccessful. The results are presented in Table IV and Fig. 6. The highest excretion of 17-ketosteroids, pregnandiol, and calcium, as per cent of calcium intake, was reached in the twenty-fifth week of pregnancy. All values decreased somewhat in the thirty-first and thirty-fifth weeks of pregnancy and decreased still more post partum. A greater similarity between changes in urinary calcium with duration of pregnancy and changes in pregnandiol and 17-ketosteroid excretion was noted using the values for per cent of calcium intake rather than absolute values in mg. per day.

TABLE IV. URINARY EXCRETION OF CALCIUM, PHOSPHORUS, 17-KETOSTEROIDS AND PREGNANDIOL DURING PREGNANCY

WEEK OF PREGNANCY	WEIGHT IN KG.	CALCIUM INTAKE* GM./DAY	CA MG./DAY	P MG./DAY	17-KETO-STERIODS MG./DAY	PREGNANDIOL MG./DAY
8	49.6	1.43	225	731	6.7	4.6
10	49.2	1.33	245	624	6.3	5.9
13	50	.86	234	568	4.8†	8.9
19	52.3	1.33	341	799	6.2	19.3
25	53.2	.79	263	855	12.7	37.2
31	55.9	.96	297	853	5.0†	25.9
25	58.2	1.20	272	971	9.5	27.6
Post partum						
4	52.0	1.00	153	1039	5.6	—

*Calcium intake estimated from standard tables of food analysis.

†Single values.

It has not been possible for the authors to continue the study of this phase of the problem. The data obtained from the one subject are suggestive that the postulated relationship between sex hormones and urinary calcium excretion will hold. Further investigation of these apparent relationships between calcium metabolism and the sex and other hormones should be undertaken. An individual variation in hormone balance would appear to be a logical explanation for the variations in normal levels of urinary calcium, and for the differences in time of appearance and height of the peak excretion in pregnancy. Assignment of the major role in determining the level of urinary calcium excretion to any single hormone or combination of hormones would be merely speculative at this time.

Summary

The urinary calcium of pregnant women increases to a maximum which is reached some time after the twentieth week and may not be attained until term. For most women, maximum values for $\frac{\text{urine Ca} \times 100}{\text{intake Ca}}$ are usually above the mean and often above the maximum normal values. The urinary calcium drops abruptly after parturition and remains below the mean normal value during the first few months of lactation. Lactation for excessive periods may be accompanied by heavy loss of calcium in the urine. Further study is indicated to determine the roles played by the various sex hormones, the adrenals, and the parathyroids in these changes in urinary calcium excretion.

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AN EVALUATION OF THE RANA PIPIENS MALE FROG PREGNANCY TEST

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SINCE the first publications appeared some time ago concerning the use of common male *Rana pipiens* frogs for pregnancy testing, our laboratory has been using this animal routinely for this purpose. Each urine specimen was run with two male *Rana pipiens* frogs at different dose levels, along with a modified Aschheim-Zondek rat test and also a *Xenopus laevis* female frog test. Our original intention was simply to gain experience with the new technique but we continued running duplicates in an attempt to clarify the equivocal observations occasionally seen. The data presented here represent our observations over a period of almost two years with 400 diagnostic cases, each of which was run with three pregnancy tests. In addition, the optimum conditions for conducting the *Rana pipiens* male frog pregnancy test were thoroughly investigated.

Methods

Only clean, concentrated morning urine specimens of at least three or four ounces were employed. Most of the patients represented real diagnostic problems in which the symptoms were conflicting and the diagnosis necessarily deferred.

Pregnancy-Test Techniques Employed.—

For the *Rana pipiens* male frog test we used untreated clean morning urine as suggested by Galli Mainini¹ and Wiltberger and Miller.² The urine was injected subcutaneously into the dorsal lymph sac. Two animals were used routinely with 2.5 ml. and 5.0 ml. volumes injected. A diligent effort, usually rewarded, was made to secure urination by gently squeezing the animal immediately prior to each examination of the urine. While the animals were on test they were contained in all-glass two-quart jars. By tilting the jar, ample quantities of urine could be taken up in a clean pipette and transferred to a ringed microscope slide for inspection under the low-power objective. The spermatozoa are easily distinguishable from the debris and frog red cells occasionally seen in the urine. Some experience is required, however, to differentiate between the spermatozoa and certain types of parasites which many of the frogs carry in large numbers.

To determine the feasibility of using blood serum in lieu of urine for the *Rana pipiens* test, a series of 40 known pregnant clinic patients all less than four months pregnant was selected at random and a urine and blood specimen taken from each. The urine specimens all produced satisfactory positive reactions in each of two duplicate animals, but when the sera were injected into a second series of frogs many of the animals suffered severe reactions. Out of

80 frogs injected in duplicate with the sera, only 50 animals produced spermatozoa. Of the remaining 30 animals, 28 were affected severely and died within three to five hours. The serum toxicity was not confined to any particular sera, since even the surviving animals were apparently depressed by the serum injections.

For the *Xenopus laevis* frog test we used the technique of Weisman, Snyder, and Coates³ with the adsorption-concentration procedure suggested by Scott.⁴ The 2 to 3 ml. of concentrate were injected into the dorsal lymph sac and the extrusion of eggs observed over a period of at least twenty hours.

We employed a five-day dosage, single-rat modification of the original Aschheim-Zondek test. A positive end point was assumed if the ovaries were significantly enlarged and hyperemic. We realize that employing one animal does not provide the accuracy of the traditional Aschheim-Zondek mouse test, but this modification has given us satisfactory results for many years, prior to the introduction of the frog tests.

Results

At least one urine specimen was run on each of 400 patients on whom an accurate final diagnosis was later obtained. Each specimen was examined with the use of two *Rana pipiens* frogs, a *Xenopus laevis* frog and also a rat. Thus three separate biologic pregnancy tests have been run on 400 urine specimens and a summary of the data is shown in Table I.

TABLE I. SUMMARY OF TEST RESULTS

TEST RESULT	FINAL DIAGNOSIS	BIOLOGIC TEST		
		RANA	XENOPUS	RAT
Positive reaction	Pregnant	149	146	124
Negative reaction	Not pregnant	228	228	227
Positive (false)	Not pregnant	2	2	3
Negative (false)	Pregnant	21	24	46
Per cent accuracy		94%	93%	88%

Of 149 correct positive *Rana pipiens* reactions, 147 were positive in both animals, and only two specimens yielded a positive reaction in only one of the two frogs. The reacting frogs in these two cases had received the higher dose level and yielded very weak positive reactions. In one of these two cases, the one reacting animal barely detected an early pregnancy (42 days from last menstrual period) and the remaining animals all gave (false) negative reactions. In the second case, the one reacting animal gave only a weak positive reaction, while the *Xenopus* gave a very weak positive (about 8 to 10 eggs in twenty hours) and the rat a false negative response at 62 days from the last menstrual period. In this case, two previous specimens taken at 48 and 52 days from the last menstrual period were uniformly negative in all animals. Therefore, out of 400 specimens each run with two male *Rana pipiens* frogs, there were only two disagreements between the duplicate animals.

There were two cases in which both male frogs were positive and disagreed with false negative *Xenopus* and rat reactions. One patient was 163 days from her last menstrual period and yet the male frog test was still weakly positive. A second patient began to bleed and presumably miscarried at about three months. At this time the *Xenopus* frog and rat tests had become negative, although both *Rana pipiens* frogs still reacted positively. A test done on this patient three weeks previously had been uniformly positive in all animals and she was clinically presumed to be pregnant at that time.

Therefore, of these four discrepancies among the frogs, the male frog test was somewhat more sensitive than the *Xenopus* test. If the male frog test were

actually the more sensitive of these two tests then this test should become positive first and remain positive longest. In general, the agreement between the two frog tests was excellent and the only significant animal discrepancies occurred with the rat. The rat test was in sole disagreement in an additional 22 specimens of which 21 were definitely false negative responses. The rat test was significantly less sensitive than either of the frog tests.

The false positive reactions deserve comment. There was one weak positive reaction in the rat which was probably erroneous because it was not confirmed by either of the frog tests. There were two additional specimens, however, which were uniformly positive with all four animals. One case was that of a patient not yet menstruating who was nursing her infant six months post partum. A second case was of a patient with a long history of irregular bleeding who could have been pregnant and miscarried.

There were 21 false negative reactions in which all four animals failed to detect any hormone. The date of the last menstrual period was accurately known in 20 of these 21 false negative reactions. These cases can be divided into two groups on the basis of the time elapsed from the last menstrual period.

TABLE II. FALSE NEGATIVE REACTIONS

SPECIMEN NUMBER	DAYS FROM LAST MENSTRUAL PERIOD	
	TOO EARLY	TOO LATE
49		211
142	66	
160		194
164		131
189	3	
192		149
196	37	
197		132
210		163
223		175
231		140
237	52	
239	71	
250		123
298	48	
306	40	
369		114
410		107
435		105
476	42	
Average 45		Average 145

Each of these false negative reactions was uniformly negative with all animals. In view of the distinct grouping of the data shown in Table II, it seems probable the time of taking the test specimen was inappropriate.

If the data from the obviously less sensitive rat test are excluded, the agreement between the results of the *Rana pipiens* and *Xenopus* frogs is nearly perfect. Since most of the false negative frog reports showed consistent agreement among both *Rana pipiens* frogs and the *Xenopus* frog, it seems reasonable to conclude the reactions were incorrect only because there was no chorionic gonadotropic hormone in the urine at the time of running the test. The exclusion of these not unexpected failures would yield a percentage of accuracy for either of the two frog tests of upward of 99 per cent accuracy. It would appear that a very serious source of error connected with all biologic pregnancy tests lies in the timing of taking the test specimen.

Comparative Sensitivity of Three Biologic Pregnancy Tests

The relative sensitivity of the three tests to the hormone or hormones found in early pregnancy urine was determined by concurrently running suitable aliquots of serial dilutions of known positive urines. The highest dilution of urine giving a positive reaction with each of the three test animals is shown in Table III.

TABLE III. HIGHEST URINE DILUTION YIELDING POSITIVE REACTION

SPECIMEN NUMBER	TEST ANIMAL		
	RANA	XENOPUS	RAT
1	1:20	1:12	1:2
2	1:50	1:12	1:2
3	1:60	1:25	1:20
4	1:45	1:30	1:20
5	1:35	1:12	1:12
6	1:45	1:25	1:12
7	1:35	1:20	1:12
8	1:50	1:25	1:20
9	1:35	1:20	1:6
10	1:70	1:40	1:30
11	1:45	1:20	1:6
12	1:40	1:25	1:12
13	1:65	1:30	1:20
14	1:55	1:35	1:25
15	1:55	1:30	1:25
Average titers	1:47	1:24	1:15

The differences between the three group means are statistically significant and indicate a ratio of sensitivity of 2:1:0.6 between the *Rana pipiens*, *Xenopus laevis*, and rat tests, respectively.

Strength of Rana Pipiens Response

It has been stated by Wiltberger and Miller² that there are no intergrades of response. While it is true the presence of spermatozoa almost invariably indicates pregnancy, there are definite variations in the strength of the response. We have arbitrarily graded the concentration of the spermatozoa as +, ++, +++, or ++++ response. Enough specimens have been diluted out and run quantitatively to indicate that if the males are uniformly healthy and active the strength of the response appears to bear a direct relationship to the titer of gonadotropic hormone. By use of an ordinary blood-cell counting chamber the urinary spermatozoa concentration has been determined in 98 positively reacting specimens and the results obtained are shown in Table IV.

TABLE IV. SPERMATOZOA CONCENTRATION IN FROG URINE

NUMBER OF SPECIMENS	ARBITRARY GRADING	RANGE OF SPERMATOZOA COUNT	AVERAGE SPERMATOZOA CONCENTRATION
			PER C.MM.
47	+	2,300-23,000	5,300
23	++	5,500-50,000	23,000
9	+++	33,000-64,000	44,000
15	++++	40,000-91,000	75,000

Two confirmed cases of hydatidiform mole produced a concentration of 110,000 and 150,000 spermatozoa per cubic millimeter, which incidentally were the highest concentrations observed in this series.

Time for Positive Reaction in *Rana pipiens*

According to Robbins and Parker^{5, 6} positive reactions in the *Rana pipiens* do not occur more than two hours following the injection of untreated urine. On the contrary Brody⁷ observed a few specimens which did not cause the release of spermatozoa before two hours, but spermatozoa were present at four hours. Bell⁸ also found some specimens which reacted only later than two hours.

The time following injection that the *Rana pipiens* showed active spermatozoa in its urine was determined by examining the frog urine at 0.5, 1.0, 2.0, 3.0, 4.0, and 5.0 hours. Before each examination the frog was gently handled and almost invariably would urinate. Two male frogs were employed each time, with 2.5 ml. and 5.0 ml. urine used. The times at which spermatozoa were first seen in 147 positively reacting urines injected into each of two frogs are shown in Table V.

TABLE V. TIME FOR POSITIVE REACTION IN MALE RANA PAPIENS AT TWO DOSE LEVELS

2.5-Ml. Dose Level.—						
Hours after injection	0.5	1.0	2.0	3.0	4.0	5.0
Number of frogs	7	15	32	51	26	16
Per cent distribution	5%	10%	22%	34%	18%	11%
5.0-Ml. Dose Level.—						
Hours after injection	0.5	1.0	2.0	3.0	4.0	5.0
Number of frogs	17	36	39	30	14	11
Per cent distribution	12%	25%	26%	20%	10%	7%

As might be expected, the higher dose level produced a quicker response. At the 2.5-ml. level 37 per cent of the positive responses occurred prior to the third hour, while at twice this dosage (5.0 ml.) 63 per cent of the positive reactions had already occurred. A significant number of positive reactions occurred between the fourth and fifth hour at both dose levels. All of the apparent negatives at the end of five hours with the male frogs were confirmed by both the *Xenopus* female frog and the rat test. After completing these experiments, we routinely began making the final check for spermatozoa in the frog urine five hours following injection. When, as occurs commonly, the spermatozoa are detected earlier, there is no need for further examination. Since the agreement between the duplicate animals was nearly perfect, we have subsequently injected 4 ml. of urine into at least two or preferably three animals. Disagreements between the duplicate animals have been rare.

Length of Rest Period Required Between Injections

The number of times a single male frog may be used for pregnancy testing has apparently not been definitely established. The frogs have been arbitrarily discarded after one test or rested a week or more before reuse. In order to find the maximum capacity of these animals for response we repeatedly injected a large group of animals with known positive urines and examined their urine for spermatozoa at regular intervals thereafter. The urines were examined at 5, 18, 26, 34, 52, 60, and 73 hours following injection and the time at which the urine became free of spermatozoa was noted.

As soon as it had been definitely established that the frog urine no longer contained spermatozoa the animal was reinjected with another 5 ml. of the same positive urine and routinely checked as before. The rest period between the finding of sperm-free urine and the next injection necessarily varied somewhat but was always 24 hours or less. This routine was repeated until each animal showed no spermatozoa at the first routine examination (i.e., at 5 hours), which indicated that it had not responded to the last injection.

A total of 17 different positive urines was employed for these experiments with groups of five or six animals receiving each specimen. The data from 95 animals repeatedly injected are detailed in Table VI, where the number of animals whose urine became sperm free at the indicated times is shown.

TABLE VI. ABILITY TO RESPOND TO REPEATED URINE INJECTIONS

TIME TILL URINE BECAME SPERM FREE	NUMBER OF INJECTION					
	1ST	2ND	3RD	4TH	5TH	6TH
5 hrs.				22	55	18
18 hrs.			3	35	11	
26 hrs.		7	49	31	7	
34 hrs.	38	60	35	6		
52 hrs.	41	26	8	1		
60 hrs.	8	2				
73 hrs.	8					
Number failing to respond	0	0	0	22	55	18
Total animals injected each time	95	95	95	95	73	18

All animals whose urine was free of spermatozoa at five hours were considered as not responding since their urine was sperm free at zero time when the animal was reinjected. All 95 animals responded up to and including the third injection, but after the fourth injection only 73 animals responded and after the fifth injection only 18 animals responded. The remaining 18 animals all failed to respond following the sixth injection. Therefore, all these animals had responded to a positive urine three times within about five days. Indeed, when all 95 animals were reinjected for the fourth time, all but 22 animals responded. As might be expected the strength of the response became weaker with successive injections. There was no question of the presence of spermatozoa up to and including the fourth, although the fifth injection resulted in only a weak positive in those animals still reacting. All animals survived this regimen. After completing these experiments we began routinely to rest our male frogs one week before reuse and subsequent experience has shown this to be satisfactory.

It was found with some urine specimens that each repeated injection produced a relatively long period of urinary spermatozoa while with certain other urines the animals became sperm free relatively quickly regardless of the number of the injection. These relative differences in the duration of response observed between whole groups of frogs were presumed to be due to differences in chorionic gonadotropin titer in the various urines employed.

Specificity of Response

The specificity of the male *Rana pipiens* reaction was determined by injecting into the animals various drugs and hormones commonly used therapeutically on pregnant women. A comparatively large dose of each substance was injected into each of 50 male frogs and the presence of spermatozoa in the urine determined. No production of spermatozoa was noted from estrone,^a progesterone,^b diethylstilbestrol,^c thyroid extract,^d caffeine citrate,^e or acetyl-

a. Estrone (aqueous suspension 2 mg.) made isotonic with NaCl, 1 ml. injected=20,000 I. U., Abbott Laboratories.

b. Lipo-Lutin (oil solution of progesterone) 1 cc. = 2 I. U. injected. Parke, Davis & Company.

c. Diethylstilbestrol U. S. P., 1 mg. suspended in 5 ml. Frog Ringer's injected.

d. Thyroprotein, 0.5 ml. = 1.25 mg. injected, Parke, Davis & Company.

e. Caffeine citrate U. S. P., 14 mg. suspended in 1 ml. Frog Ringer's injected.

salicylic acid.^f None of the animals were apparently affected by these various substances and all survived the injections. In each of fifty animals a strong positive response was noted with epinephrine^g as reported by Robbins and Parker.⁹ Several frogs were killed by doses above 0.1 ml. of 1:1,000 epinephrine however.

We were fortunate to have available for comparative assay some pituitary follicle-stimulating hormone concentrates prepared from menopausal urines.* The strongest specimens were selected with titers of 128 to 256 mouse uterine hypertrophy units. Single injections of a total of 64 up to 150 mouse gonadotropin units failed to produce urinary spermatozoa in about a dozen different frogs. Since each of these injections represented the total FSH contained in at least one-half an entire 24 hours' urine output of these patients, the possibility of a false positive response in a menopausal patient would appear to be unlikely.

The possible depressing effect of several commonly used sedative drugs on the *Rana pipiens* reaction was investigated by adding relatively large quantities of acetylsalicylic acid,^h P-A-Caffeineⁱ and phenobarbital^j to known positive urines and injecting the prepared urine into a series of animals. A total of 60 animals each responded to 5 ml. of known positive urine containing 160 mg. acetylsalicylic acid (one-half 5-grain tablet). Another series of 100 animals gave uniformly positive reactions to 5-ml. doses of known positive urines containing P-A-caffeine. When phenobarbital was employed the frogs became somewhat drowsy but each of 100 animals receiving the prepared 5-ml. doses responded positively. Therefore, it does not appear that sedatives would interfere with a positive reaction and cause a false negative report. This series of 260 animals, incidentally, serves as a positive control group and indicates there were no females among these randomly picked animals.

Negative controls consisting of another fifty animals were injected with 5 ml. Frog Ringer's Solution and no spermatozoa were found following this treatment. An additional fifty animals, selected at random from our stock without treatment, were placed in jars and their urine examined for spermatozoa without success for a period of five hours.

Rana Pipiens Husbandry

The maintenance of healthy active frogs is essential because an animal affected with "red leg" disease and/or more or less starved cannot be relied upon for accurate test results. The conducting of the *Rana pipiens* test is simple and so little equipment is necessary there is a tendency to neglect the proper care of the frogs. If efficient service is desired an adequate supply of animals should be constantly available. Shipments from the biological supply houses are often delayed and occasionally we have received entire orders of frogs moribund from "red leg" disease. We abandoned the practice of storing the frogs in the refrigerator because occasionally the animals seemed to be apparently insensitive following this treatment. Rose¹⁰ has stated that *Rana pipiens* cannot be maintained at refrigerator temperature without food and remain free of the various bacterial and fungus diseases to which they are subject. In storing our reserve and resting stocks of animals we have attempted to

*Through the cooperation of Drs. A. L. Heller and R. A. Shipley.

f. Acetylsalicylic acid, 160 mg. suspended in 5 ml. Frog Ringer's Solution.

g. Adrenaline (epinephrine hydrochloride) in physiological salt solution with 0.5 per cent Chloretone and 0.1 per cent Na bisulfate as preservative 0.1 ml. of 1:1,000 injected. Parke, Davis & Company.

h. Acetylsalicylic acid, 160 mg. suspended in 5 ml. known positive urine.

i. Phenacetin, 33 mg., acetylsalicylic acid 53 mg. caffeine citrate 28 mg., suspended in 5 ml. known positive urine.

j. Phenobarbital, 8 mg. dissolved in 5 ml. known positive urine.

simulate the natural environment of the frogs as closely as possible by providing a large stainless-steel tank 80 by 30 by 12 inches deep as illustrated. An overflow pipe maintains the water level at about 5 inches. This depth allows ample diving and swimming activities. Resting platforms are constructed of Plexiglass which allows a clear view for cleaning the tank and locating the animals (Fig. 1).

The frogs are fed every two or three days on mealworms and medium-sized earthworms, which are usually available at local bait shops. Some provision is essential for feeding the animals out of water since they will not partake of motionless food. Any worms which fall into the water soon drown and are thereafter ignored by the frogs. Individual animals will consume six or eight mealworms in rapid succession or they will stuff one or two four-inch earthworms into their mouths. The water in the tank is changed at least once every 48 hours.

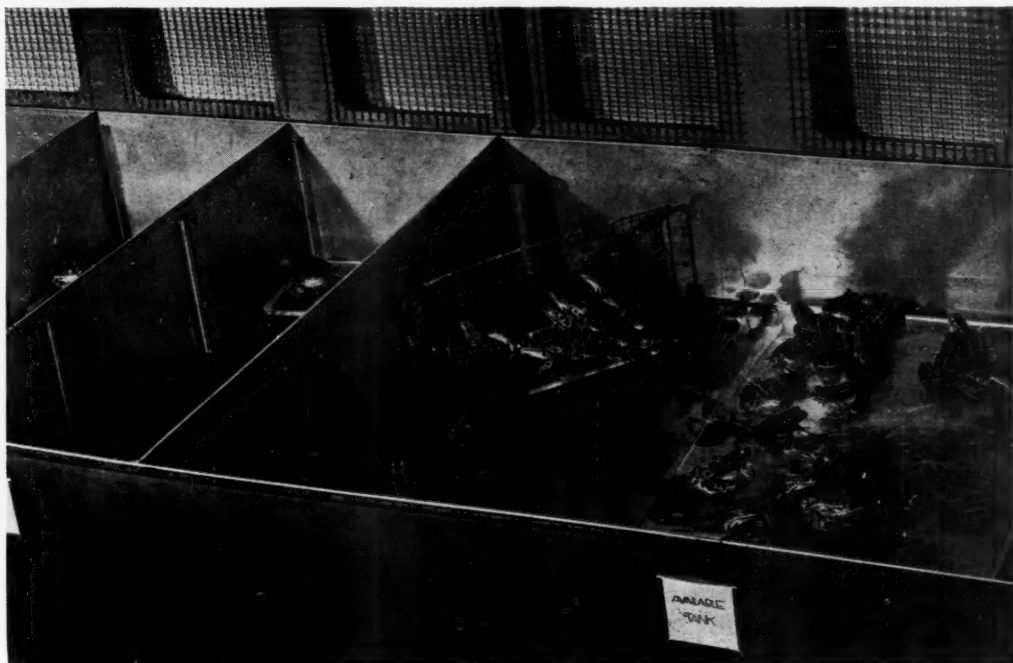


Fig. 1.—Special tank for *Rana pipiens* frogs (covers raised).

The tank is provided with aquarium grass and snails which help keep the tank clean. The frog population is usually over 150 animals and loss through death averages about three or four animals each week. We need only replenish the tank population every four or five months and all incoming shipments of new frogs are carefully inspected and prophylactically treated with sulfadiazine before use. Since we made these arrangements a mortality, either spontaneous or while on test, has ceased to be a problem.

The differentiation of sex in the *Rana pipiens* is of importance since presumably a female animal could not respond and would therefore give a false negative reaction. Brody⁷ recommends using the frogs only once, sacrificing them, and checking for the presence of gonads. While finding the gonads at autopsy is the only sure way of insuring the use of male animals we have seen so very few disagreements between the two "males" and such excellent agree-

ment between the *Rana pipiens* and *Xenopus laevis* results, that we believe if at least two or perhaps three frogs are used each time, a routine check on the sex of the animals will be sufficient. False negative reactions may also be due to the use of sick animals. Any disagreements between the animals should of course be rechecked with another frog.

Comment

The use of untreated urine was abandoned by Brody⁷ because of apparent "toxicity." Bell, Macgregor, and Vant¹¹ concluded that when urine specimens were sent long distances to the laboratory or when the urine had stood several days the high animal mortality rate precluded use of the test. They reported 36.1 per cent of their tests at the 5-ml. dosage level unsatisfactory. No preservative to discourage bacterial growth in the urine while in transit was provided by these investigators.

In our experience, death of animals while on test has become a very infrequent occurrence. It is our impression that clean, freshly voided urines are seldom "toxic" and where possible we request patients to refrigerate their specimen before delivery to the laboratory. When loss of frogs on test occurs, the urine is usually foul smelling and obviously contaminated with bacteria. There is also the real possibility of bacterial destruction of the hormone itself. The use of uncontaminated urine specimens is essential for reliable results. In the reuse experiments reported here, out of 95 frogs which were repeatedly injected with known positive urines and which ultimately became incapable of responding and noticeably wearied, not a single animal died. The total volume of urine injected into each of these animals over a period of about seven days was from 20 to 30 ml., which was equivalent to over 60 per cent of the total body weight of each frog. This amount of urine contained a significant quantity of pregnancy hormones, nitrogenous compounds, and inorganic salts.

The possibility of seasonal variation in the reactivity of the *Rana pipiens* has been suggested by several investigators. Our studies with this animal began in the early spring of 1948 and have continued to the present time. Our observations have therefore extended over two breeding seasons and we have observed no significant changes in sensitivity or strength of response which could be possibly related to seasonal influence. During the breeding season the spontaneous emission of sperm might be most likely to occur. We have detected no instance of spontaneous emission of sperm in over 350 control animals injected with various drugs and hormones. In the diagnostic series of 400 patients' urines run with duplicate animals there were only two "false positives" and there was reason to believe at least one of these was actually a pregnancy which suffered early miscarriage.

The several days' time required to carry out the modified Aschheim-Zondek rat test represents a serious objection to its use. Furthermore, some experience is required to interpret correctly the appearance of the ovaries for the end-point reading. For the *Xenopus laevis* frog test it is necessary to concentrate the hormone by some suitable technique before injection. In addition, these animals are very expensive and in spite of careful feeding and handling we have suffered a fairly high mortality rate.

On the other hand the *Rana pipiens* frog is sensitive enough to react to unprepared urine, the initial cost of the animals is negligible, and the mortality rate not serious. Furthermore, this test is the most rapid of all the biologic pregnancy tests presently available. While the use of a concentrated hormone extract with the male frog test will yield a quicker response, the preparation of the extract would seem to be an unnecessary inconvenience. The possibility that a concentration technique might raise a low titer to the point of causing

a reaction should be considered, but other factors such as period of time elapsed from conception and proper functioning of the chorionic hormone-producing tissue would seem to be more important. It is probable that all biologic pregnancy tests using test animals depend upon the chorionic gonadotropic hormone which rises sharply to high concentrations and then falls precipitously near the end of the first trimester. While false negative reactions do occur with the male frogs using unconcentrated urine, each of the false negative reactions reported in this series was confirmed by the additional animal tests run concurrently. Indeed the male frog test showed the lowest incidence of false negatives of all three pregnancy tests employed in this study.

The earliest positive reactions detected in this series occurred at 30, 34, 34, 35, 36, 36, and 40 days from the last menstrual period. Thus, these patients were about one week overdue on their first missed periods. On 13 patients, however, a negative reaction with a urine specimen taken soon after the first missed period was repeated later with a positive reaction. Each of these 13 early negative reactions showed unanimous agreement between the two male *Rana pipiens* frogs, *Xenopus laevis* female frogs, and the A-Z rat. If any one of these animals had been run alone the result would have later been classed as a "false negative." It seems improbable, however, that all four animals could fail to detect the hormone and it is more likely that in some patients the hormone appears late or is of low titer. In seven of these thirteen cases the repeat specimen showed a positive reaction with all three frogs while the rat continued to be negative. In the remaining six the repeat urine specimen was unanimously positive with all four animals.

It appears that urine specimens should not routinely be taken for biologic pregnancy testing until the patient is at least six weeks, but less than approximately fifteen weeks, from her last menstrual period. The near-perfect agreement between the results of the *Rana pipiens* and *Xenopus* frog tests indicates the very high accuracy both these animal tests can achieve. Perhaps the greatest source of error involved in "pregnancy testing" lies in the difficulty of correctly timing the test to coincide with the relatively great concentration of gonadotropic hormone which exists only transiently during the first trimester of pregnancy. This especially becomes a problem with the patient whose history of irregular bleeding makes the accurate fixing of a last menstrual date almost impossible. In these cases the pregnancy test can contribute substantial information when it is repeated.

Summary and Conclusions

1. The *Rana pipiens* male frog test for pregnancy is simple, rapid, accurate, and economical for routine use.
2. The use of untreated morning urine alone yields dependable results without the necessity of preparation of a concentrated hormone extract.
3. With doses of 2.5 to 5 ml. of untreated urine, at least 5 hours must be allowed to elapse before a negative response can be assumed.
4. Urine specimens for biologic pregnancy testing should routinely be taken only during the period from six to fifteen weeks from the last menstrual period.
5. Urine specimens for biologic assay study represent labile hormone solutions and should be handled accordingly.

The technical assistance of Mrs. June Capasso is appreciated.

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CHORIONEPITHELIOMA

A Study of Fifteen Cases

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OUR interest in chorionepithelioma has been accentuated by the admission of nine of these cases to Shreveport Charity Hospital since 1940. During that same general period of time numerous articles on the subject note mortality rates on this tumor from 7.14 per cent to 69.2 per cent.¹ Many of these reports give survival rates that are better than those usually expected in treating carcinoma of the endometrium, which, in most cases, is considered a comparatively mild type of genital malignancy. At the same time chorionepithelioma is often referred to as the "most malignant" or "most rapid growing" of malignant tumors.

In attempting to explain this paradox we have reviewed fifteen cases of chorionepithelioma. Eleven of the cases came from the files of Shreveport Charity Hospital from 1932 to 1948. Four additional cases were taken from the Pathology Department of the hospital. These were not hospital admissions but were specimens submitted for study and diagnosis. The private doctors in charge of these cases kindly made the clinical records available to us and gave their permission to use the cases in this report. There was one additional case treated in the hospital in 1934. This patient failed to complete the treatment and no follow-up was possible. She had a diagnosis of choriocarcinoma made from an excised metastatic node in the vagina. The case is not included because of insufficient data. However, it is felt that no mistake would be made in considering it a mortality.

It was interesting to note that only two cases were obtained by extending this study from 1940 back to 1932. Along the same line it was found that only one hydatidiform mole was diagnosed in the hospital between 1941 and 1944, while during that same period three choriocarcinomas were so diagnosed and treated. This inconsistent proportion of cases leaves one guessing. However, it is likewise difficult to explain the great differences in the number of cases reported from various countries or even sections of the same country.

The average age of fourteen of the patients was 25.8 years. The age of the other patient was not given. Of this group only three patients were over 30 years old, one of these being 51 years of age. Eight of the patients were Negro and seven were white.

Considering the mortality on the group as a whole, it would be 73.3 per cent. However, of the cases classified as choriocarcinoma the mortality was 100 per cent and the mortality of the chorioadenoma and syncytioma group was nil.

In comparing this series with most others that have been grouped in the same manner, we find a disproportionate number of choriocarcinomas. We feel that this fluctuation in the types of chorionepithelioma largely explains the wide range of figures published for survival rates. In the next ten years

we might just as easily have eleven cases of the less malignant variety and four cases of the choriocarcinoma group which, if classified under the misleading term *chorionepithelioma*, would completely reverse our survival rate without improvement in diagnosis or treatment.

Syncytioma or Syncytial Endometritis

We had only one case which fell in this category. Hertig and Sheldon² cast doubt as to whether this type of tumor should even be considered as chorionic malignancy. Nevertheless, it must be included in a study of this type because the literature contains many instances of this tumor reported as *chorionepithelioma* with the authors taking credit for cures by early diagnosis and hysterectomy.

More recently reports are being made in which these cases have been followed to complete recovery with no treatment other than curettement.³

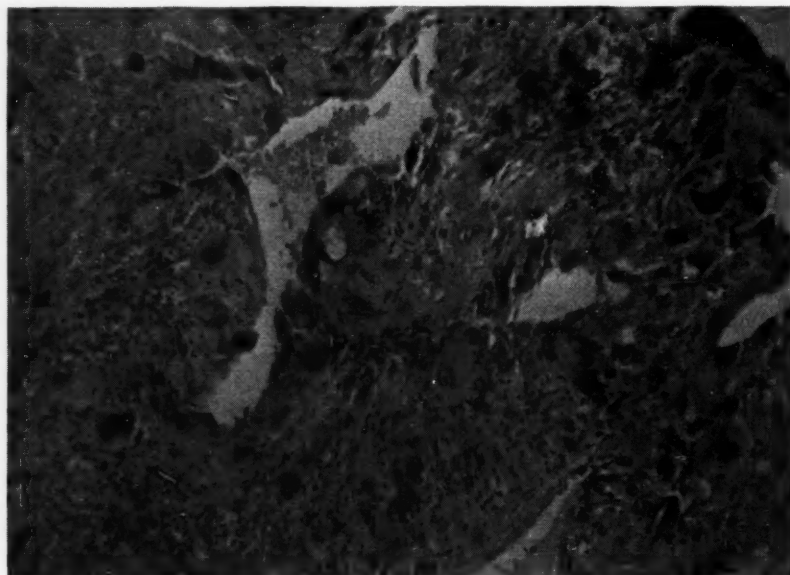


Fig. 1.—Syncytioma. Note the giant syncytial cells invading the myometrium associated with marked cellular inflammatory reaction.

This case was one from outside the hospital. It occurred in a 20-year-old white woman and apparently followed an early abortion. The doctor who submitted the uterine scrapings suspected "mole or chorionepithelioma." Dr. W. R. Mathews of our Pathology Department felt that the sections looked more like chorioadenoma but did not think that choriocarcinoma could be excluded from the scrapings alone.

The uterus and tubes were removed and were originally reported as showing choriocarcinoma because of the invasion of the myometrium and the total absence of villi. However, in reviewing these slides Dr. Mathews noticed that there were practically no Langhans' cells present and that the endometrium and myometrium showed a great deal of inflammatory reaction. This made the case fit Ewing's classification of syncytioma rather nicely.⁴ Therefore the diagnosis was revised to syncytioma probably originating as chorioadenoma. Since there had been this reversal of opinion the slides were submitted to Dr. Emil Novak and he also made the diagnosis of syncytial endometritis.

Chorioadenoma Destruens

This variety of chorionic malignancy is also known as invasive mole or malignant mole. It carries an excellent prognosis and clinical metastases are

almost unknown. Removal of the uterus is the only treatment necessary. The danger of death from this tumor is by perforation of the uterus, with hemorrhage and infection.

This series included three chorioadenomas, two of which followed hydatidiform moles and the third followed an early abortion. The interval between the passage of the mole or pregnancy and the diagnosis was eight weeks, six weeks, and six months, respectively.

Two of these cases had positive curettings as a basis for hysterectomy. The third case had operation two months after passage of a hydatidiform mole on the strength of a positive Friedman test and abnormal bleeding. All patients had total hysterectomy. Two patients had bilateral salpingo-oophorectomy as well. This we feel was unnecessary, especially since one of the patients was 19 years old. The other patient was 37 years old and the loss was not so great.

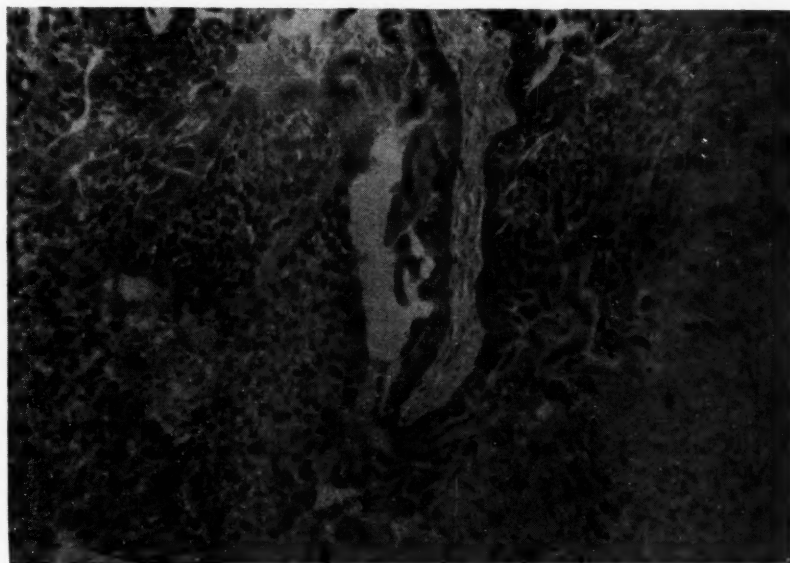


Fig. 2.—Chorioadenoma. Note the preservation of chorionic villi, orderly arrangement of syncytium and Langhans' cells.

The latter patient was given postoperative x-ray, 3,200 r to six ports over the pelvis, epigastrium, and chest, front and rear. This was done because the first microscopic study of the specimen was not clear-cut chorioadenoma. At present the x-ray treatment would not be given even in doubtful cases.

These three patients are living and well in 1950. The original operations were done in 1946, 1947, and 1947. Two of these cases showed small lutein cysts of no clinical significance.

Choriocarcinoma

The prognosis and clinical comparison of this group as compared to the other two would be similar to comparing an early skin cancer to a melanoma. This is the rare, fatal chorionic malignancy that is usually brought to mind by the term chorionepithelioma.

Of the eleven cases of choriocarcinoma studied, nine were from the hospital records and two were outside cases followed in our laboratory.

Microscopically these tumors were recognized by the wild growth of masses of trophoblastic cells invading the uterine muscle with destruction of

tissue and liberation of blood in tissue spaces. In none of our cases were villi present. The mortality in cases showing these microscopic findings was 100 per cent in this series.

TABLE I. SUMMARY OF DATA ON CHORIOADENOMA AND SYNCYTIOMA

CASE AGE RACE	TYPE OF PRECEDING PREGNANCY	TIME INTERVAL FROM PREG- NANCY TO SYMP- TOMS	TIME INTERVAL FROM PREG- NANCY TO DIAGNOSIS	TYPE OF TREATMENT	TIME INTERVAL OF FOLLOW-UP FROM TREATMENT
<i>Syncytioma.</i> —					
1 20 years White	Probably early abortion*	2 months	3 months	Bilateral salpingo- oophorectomy Total hysterectomy	4 years, 1 month
<i>Chorioadenoma.</i> —					
2 White	Hydatidi- form mole	8 weeks	8 weeks	Total hysterectomy	3 years, 2 months
3 37 years White	Probably early abortion*	Immedi- ate	6 weeks	Total hysterectomy, bilateral salpingo- oophorectomy X-ray to pelvis, epigas- trium, and chest	1 year, 9 months
4 19 years White	Hydatidi- form mole	3 months	6 months	Total hysterectomy, bilateral salpingo- oophorectomy	2 years, 6 months

*These patients had histories suggesting early abortion but both had uterine scrapings which showed chorioadenoma structure.

From Table II it may be seen that the interval between diagnosis and the preceding pregnancy was quite variable. The time interval between the appearance of symptoms and diagnosis was longer than it should have been in every instance. The responsibility for this is about equally shared by the patient and the doctor.

Case 10 was the only case in which a careful search for metastatic lesions revealed none to be present before the time of operation. It is likely that small, unrecognizable metastatic lesions were present in the lungs of this patient because they were easily demonstrable one month after operation.

We believe this lends strength to Hertig's suspicion that the malignant process may be under way even before the responsible pregnancy has been expelled from the uterus. Douglas and Otts⁵ have reported an undoubted case of this type.

Metastasis.—In a study of the autopsies which were done on eight of the eleven patients metastatic lesions were found in the following organs: lungs, liver, vagina, brain, kidneys, bladder, urethra, ovary, skin, regional nodes, ileum, jejunum, large bowel, spleen, and meninges.

Curettement.—Curettement as a method of diagnosis in these cases has been discussed because of the possible dangers. It has also been pointed out that it may not reach the tumor. The danger of curettage causing spread is somewhat theoretical and will be difficult to prove. However, we have ample proof that the method is fallible as a diagnostic procedure. In this choriocarcinoma group four curettements were done. One of the four failed to reveal tissue that would furnish the diagnosis because the tumor mass was deep in the wall of the uterus.

From autopsy findings it is evident that in at least five of the eleven cases curettage would have been of no help in diagnosis. Two of these had the tumor

TABLE II. SUMMARY OF DATA ON CHORIOCARCINOMA

CASE AGE RACE	TYPE OF PRECEDING PREGNANCY	TIME INTERVAL FROM PREGNANCY TO SYMPTOMS	TIME INTERVAL FROM PREGNANCY TO DIAGNOSIS	TYPE OF TREATMENT	TIME INTERVAL FROM TREATMENT TO DEATH
5 26 years Negro	Hydatidiform mole	18 days	2½ months	Total hysterectomy, bilateral salpingo- oophorectomy	16 months
6 24 years White	Abortion early	12 months	27 months	None	Autopsy Diagnosis
7 31 years Negro	Abortion early	3 months	5½ months	X-ray to pelvis	2 months
8 18 years Negro	Term preg- nancy	Immedi- ately	2½ months	Total hysterectomy, rt. salpingo- oophorectomy X-ray to chest	3½ months
9 21 years Negro	Term preg- nancy	4 months	8 months	Total hysterectomy, bilateral salpingo- oophorectomy X-ray to pelvis and chest	2 months
10 25 years White	Term preg- nancy	27 months	31 months	Total hysterectomy, bilateral salpingo- oophorectomy X-ray to pelvis and chest	9 months
11 24 years Negro	Hydatidiform mole	Unknown	17 months	None	Autopsy Diagnosis
12 20 years White	Hydatidiform mole	9 months	10 months	Supravaginal hysterec- tomy, bilateral salpingo-oophorectomy	12 days
13 20 years Negro	Stillborn (6 months)	1 month	4 months	Total hysterectomy, bilateral salpingo- oophorectomy X-ray to pelvis and chest	3½ months
14 26 years Negro	Tubal ectopic pregnancy	1 month	4½ months	None	Autopsy Diagnosis
15 51 years Negro	Tubal ectopic pregnancy	7 months	11 months	None	Autopsy Diagnosis

in the tube. In three others the lesion was deep in the uterine wall and not accessible to the curette.

Biologic Tests.—The biologic tests for pregnancy are likewise not infallible as a diagnostic method in these cases. This is especially true of the spinal-fluid Friedman test. Case 8 in this group had repeated positive urinary Friedmans, but failed to show a positive spinal-fluid Friedman with 10 c.c. of spinal fluid even when the patient was riddled with metastatic lesions.

In Case 10 the urine gave a positive Friedman test three times. The spinal fluid was positive before removal of the uterus then became negative after operation. The urinary Friedman on the other hand remained positive after removal of the uterus, tubes, and ovaries and this was before any metastatic lesions were demonstrable. This, in a rough way, indicates that the spinal-fluid Friedman test is a poor substitute for the quantitative Friedman. The amount of tumor

tissue required to produce enough of the hormone to give a positive biologic test does not appear to be comparable in any two cases.

Case 13 had positive urinary and spinal-fluid Friedman reactions both before and after operation. This is more the expected thing since widespread metastasis was present from the beginning.

It was interesting to see that in Case 5 the urinary Friedman remained negative until twelve months after operation. This patient had a chest x-ray that revealed early metastatic lesions in the lungs the day after operation. The x-ray was repeated with the same findings twenty days after operation. A third film with the same findings was made forty days postoperatively. Sixty-three days after surgery another chest x-ray was made and the metastatic lesions were no longer present. At five months another negative chest x-ray was reported. The next chest x-ray was made 12 months after operation and at this time it was reported as positive for a single area of infiltration 2.5 cm. in diameter in the right second interspace in the midclavicular line. When the metastatic lesion reappeared the urinary and spinal-fluid Friedman tests became positive for the first time.

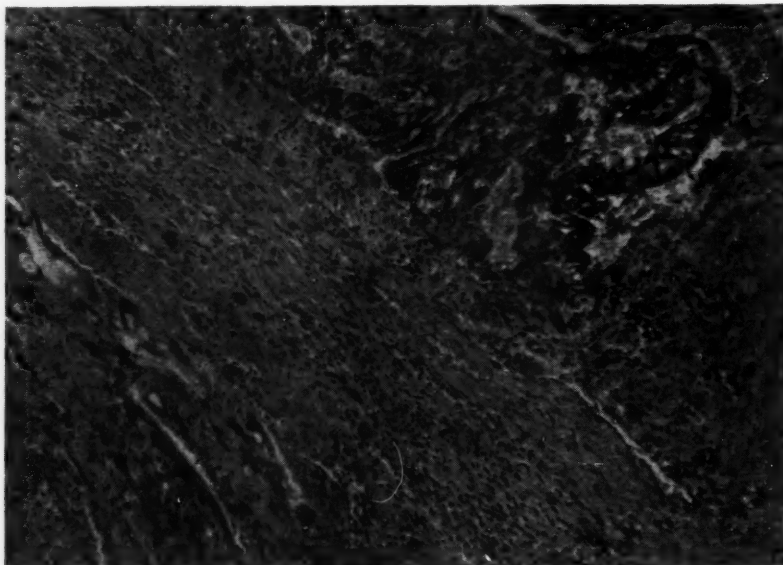


Fig. 3.—Choriocarcinoma. Note the groups of Langhans' cells and syncytial cells infiltrating the myometrium and the absence of preserved chorionic villi.

The biologic test is a definite aid in diagnosis but, as Park and Lees⁶ emphasize, it must be interpreted in the light of the clinical findings.

Lutein Cysts.—Lutein cysts were palpable in only one case. In three cases there was gross enlargement in the pathological specimen or at autopsy. No record of microscopic lutein cysts was made. The ovaries should not be removed because of the presence of these benign cysts that may accompany chorionepithelioma or hydatidiform moles.

Symptoms.—The presenting symptom was abnormal and excessive bleeding in nine of the eleven cases. This bleeding varied from a prolonged bloody discharge to an exsanguinating hemorrhage. The two patients who did not have abnormal bleeding as a chief complaint complained of abdominal pain. One of these had chills and fever, apparently due to a complicating pelvic cellulitis. All patients except one had some abnormal bleeding and that one had the tumor in the tube.

Cause of Death.—The cause of death in these patients varied with the type of metastasis. Four of the patients died of generalized metastases. One died of lung metastasis with abscess formation. Another died of pneumonia. The two most unusual deaths were from rupture of the liver at the site of metastasis with fatal hemorrhage into the abdominal cavity. Two died of hemorrhage from vaginal metastasis. In one case the cause of death is not known.

Type of Preceding Pregnancy.—Another different and interesting finding in this series was that only three of the choriocarcinomas followed hydatidiform mole. Of the remaining eight cases, three followed abortion, three followed full-term pregnancies, and two followed tubal ectopic pregnancies. This serves as a reminder that chorionic malignancy may develop anywhere a pregnancy can develop. It is true that in general 50 per cent of chorionepitheliomas follow hydatidiform mole but this figure cannot be taken too literally in considering individual cases or small series.

It is even more unusual that in a series as small as this two cases should follow tubal ectopic pregnancy. Assuming that chorionic malignancy is no more prone to develop in the Fallopian tube than in the uterus, the mere ratio of tubal pregnancy to uterine pregnancy would make choriocarcinoma of the tube an exceedingly rare tumor.

Case histories of two of these patients are given because they are rather typical of our hospital admissions and also because one of these patients showed metastasis to the tip of her nose.

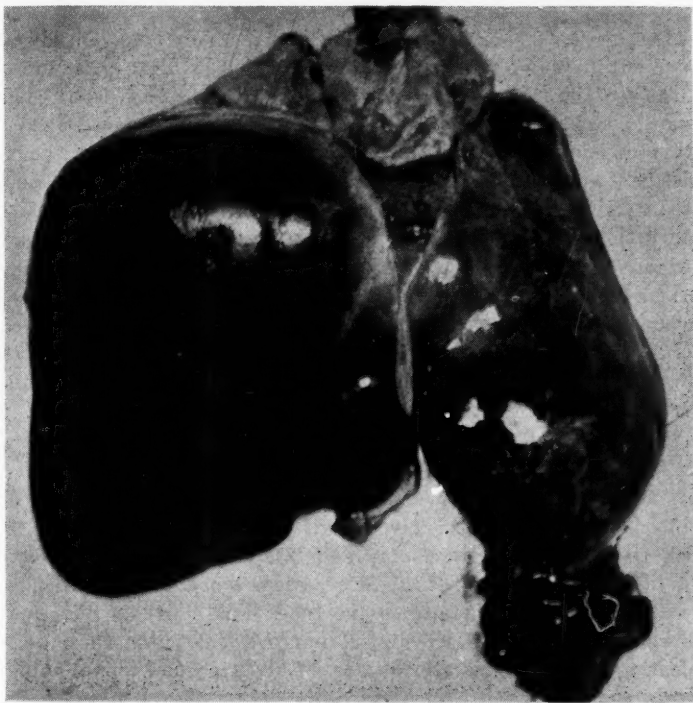


Fig. 4.—Metastatic choriocarcinoma in the liver causing rupture of the liver and fatal hemorrhage.

CASE 8 (434784).—D. J., an 18-year-old colored woman, was admitted to the hospital on Aug. 21, 1942, with a chief complaint of vaginal bleeding. She had had one pregnancy which ended in a full-term delivery by a midwife on July 12, 1942. The patient stated that she had never stopped bleeding since the delivery. Hemoglobin on admission was 5 Gm., or 32 per cent. Ergotrate, ferrous sulfate, and multiple blood transfusions were given until the hemoglobin was 64 per cent.

On Oct. 2, 1942, curettage was done and scrapings were reported suggestive of chorion-epithelioma. The urine gave a positive Friedman but the spinal fluid (10 c.c.) was negative. Chest x-ray reported one small suspicious area in the third interspace on the left side. Pelvic examination was still negative, showing no evidence of extension to the cervix, vagina, or vulva. The uterus was of normal size and position and freely movable. No adnexal masses were palpated.

On Oct. 14, 1942, a total hysterectomy and right salpingo-oophorectomy were done. The urinary Friedman remained positive but the chest x-ray had shown no change on November 2. The patient felt much better and was allowed to go home on November 12, but was to return in four weeks for a Friedman test and chest plate. The Friedman was still positive on December 16, and the patient was readmitted to the hospital. On December 28, x-ray revealed another questionable area in the sixth interspace on the right side. X-ray therapy to the chest was started and the patient received a total of 1,200 r to the two areas mentioned.

On Jan. 23, 1943, the patient began to complain of nausea and some vomiting. Palpation of the abdomen revealed a mass in the epigastrium in the region of the stomach. The liver was not felt below the right costal border. On January 26, the patient complained of severe epigastric pain for which she was given morphine. Following the hypodermic she became comatose, went into mild shock, and died in a few hours. Intravenous fluids and stimulants had no effect. Autopsy revealed that death was due to intra-abdominal hemorrhage from rupture of a metastatic tumor nodule in the liver. There were metastatic lesions of choriocarcinoma in the lungs, liver, spleen, meninges, and left kidney.

CASE 9 (44892).—O. J., a 21-year-old Negro woman, entered the hospital on Jan. 19, 1944, with a chief complaint of vaginal bleeding. She had had three full-term deliveries and no abortions. The last baby was delivered by a midwife in April, 1943. The patient progressed satisfactorily until August, 1943, when she began to have prolonged periods. From then until the time of admission she did not go longer than seven days without some bleeding. At times the bleeding was profuse though not enough to cause fainting or shock. There had been an estimated weight loss of 20 to 30 pounds with a corresponding loss of strength. There was no history of hemoptysis.

Physical examination revealed a weak, emaciated, anemic Negro woman. The skin revealed no abnormal findings on admission and the chest was negative to physical examination by the obstetrician. The liver was not palpable. Pelvic examination revealed a cervix with a bluish discoloration similar to Chadwick's sign but no evidence of metastasis or extension to the cervix, vagina, or vulva. The uterus was of normal size and position and freely movable. The ovaries were not enlarged but iliac lymphadenopathy could be palpated.

The hemoglobin on admission was 5.2 Gm., or 32 per cent. The urine and spinal-fluid Friedman tests were positive. Chest x-ray revealed numerous areas of increased density thought to be due to metastatic lesions.

Multiple blood transfusions were given until the hemoglobin reached 10 Gm. on January 29, at which time a total hysterectomy and bilateral salpingo-oophorectomy were done under local and light general anesthesia. The patient stood the operation well and on her twelfth postoperative day x-ray therapy to the lungs was started. She received a total of 1,000 r to eight ports. There was no clinical improvement but a chest plate on March 17 showed some clearing of the metastatic lesions. The urine and spinal-fluid Friedman tests remained positive.

There was suggestive evidence of mental impairment and personality change from the time of admission but neurological examination remained negative until March 7, when the patient had a light convulsion beginning in the left arm and becoming generalized. During the next two weeks she had numerous similar convulsions and on March 26 developed a flaccid paralysis of the left arm.

During the postoperative course it was noticed that the hemoglobin made a slow but definite drop (10 Gm. to 7 Gm.) without external evidence of blood loss.

On March 1, there was noticed some swelling of the tip of the patient's nose, which was first thought to be due to infection. Later, however, definite bluish nodules appeared on the tip of the nose and in the nostrils. These metastatic areas increased in size until the patient died of brain metastasis on March 27, 1944, the fifty-eighth postoperative day.

Autopsy revealed metastatic choriocarcinoma to the liver, lungs, kidneys, jejunum, brain, and nose.

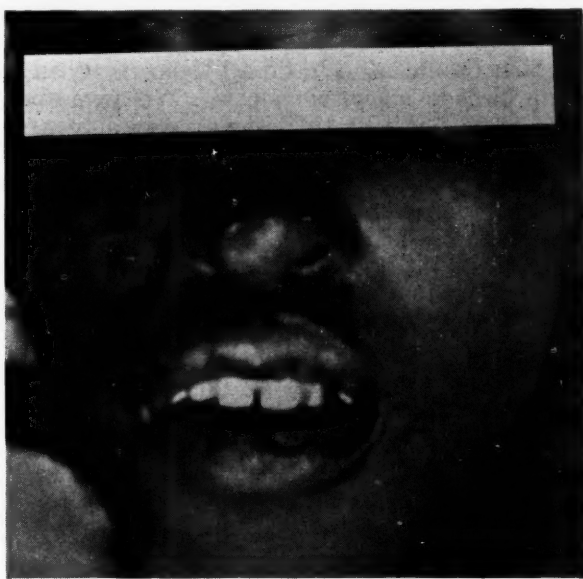


Fig. 5.—Metastatic choriocarcinoma seen on the tip of the nose.

Comment

It has been said that "good judgment comes from experience and experience comes from poor judgment." Because of the rarity of choriocarcinoma not many doctors will have the opportunity to gain good judgment soon enough to apply it by this method. Realization of this fact has brought into being the Chorionepithelioma Registry, headed by Emil Novak, which cannot be endorsed too strongly. It is hoped that all doctors will send in their surgical specimens so that uniformity in classification will be possible.

A better understanding of these tumors will give the doctor the confidence to observe the patient who shows a positive Friedman test one to three months after the passage of a hydatidiform mole. Many uteri must have been sacrificed in the hope of curing choriocarcinoma while it was early when actually a true malignancy was never present. It is good that we have molar pregnancies to put us on guard against chorionic malignancy. At the same time, "overdiagnosis" and hasty surgery should be avoided.

Our group of cases reveals the importance of suspecting chorionic malignancy in any and all pregnancies that are followed by abnormal bleeding. Naturally it will be an extremely difficult diagnosis when it follows ectopic pregnancy.

We feel that when surgery is indicated in any of these patients, the ovaries may be spared, and especially is this true in the young patients. The ovary has not been a frequent or early site of metastasis and when metastasis is present in the ovary it is also present in many more important and inaccessible sites.

The use of x-ray in our experience has been very disappointing. In almost every case the tumor "grows in the ray" and usually metastatic lesions have not been reduced by this treatment regardless of how accessible the lesion might be.

It may be argued that in this series the patients who survived did so because they had earlier diagnoses and treatment. If we had had just one case with a microscopic diagnosis of choriocarcinoma survive we might entertain that suggestion. However, as these cases have turned out, we think that Ewing⁴ was very nearly right when he said that he had never seen a case of choriocarcinoma get well.

Some may question the decision to do a hysterectomy in these patients with choriocarcinoma who already show metastasis. We have operated on these patients with no hope of the metastatic lesions regressing after removal of the parent tumor, although it did temporarily occur in one case. However, surgery does prolong the life somewhat by preventing early death from uterine hemorrhage. It also prevents the severe secondary anemia which would make the patients liable to early death by intercurrent infection. That is about all that our treatment has accomplished in this malignant group.

Summary

1. Fifteen cases grouped under the diagnosis of chorionepithelioma are presented.

2. It is pointed out that the mortality in these patients depends more on the proper classification of the tumors than on the treatment.

3. In our experience choriocarcinoma has been uniformly fatal. On the other hand there has been no mortality in the chorioadenoma and syncytioma group.

4. X-ray is of little or no value in treating choriocarcinoma or its metastatic lesions.

5. Total hysterectomy is curative in the chorioadenoma and syncytioma group. Its chief value in the choriocarcinoma group is preventing early death from uterine hemorrhage. Also it prevents death from intercurrent infection in the face of a severe secondary anemia such as may be seen when the bleeding uterus is left in place.

6. The presence of metastasis is no contraindication to surgery.

7. Mistakes will be minimized if every doctor who encounters a case of this type will submit his surgical specimens to the Chorionepithelioma Registry.

1753 LINE AVENUE

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TIME, SITE, AND TREATMENT OF RECURRENCES OF ENDOMETRIAL CARCINOMA

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MOST reports on endometrial carcinoma deal with treatment and the 5-year survival. Although carcinoma of the endometrium has the most favorable prognosis of all cancers of the female genital tract, the progression of persistent cancer or the recurrence after apparently complete extirpation of cancer reduces this survival rate. A study of some of the factors which influence the time, the anatomical site, and the treatment of such recurrences may decrease their frequency.

Time and Number of Recurrences

Two hundred sixty-six patients with carcinoma of the endometrium were treated at the Woman's Clinic of the New York Hospital from 1933 through 1949. Two hundred sixty received their initial treatment here, while 6 patients had been treated elsewhere first. Forty-nine (18.4 per cent) had persistence or recurrence of endometrial cancer; 12 (4.4 per cent) had persistence, while 37 (14 per cent) had recurrence.

A distinction is made between simple persistence with progression of carcinoma and recurrence of carcinoma. Persistence is the inevitable progression of cancer which has either not been treated or has been incompletely treated by irradiation or surgery, so that obvious cancer remains. Such progression occurred rapidly, usually within 6 months. It was in close anatomical relationship to the original site. The carcinoma usually showed widespread extension at the time of the original treatment and was usually a highly malignant, undifferentiated histological type. Recurrence, however, is the reappearance of carcinoma after apparently complete extirpation. It may occur within 6 months after treatment, but usually did not appear until later. While it may be close to the site of the original cancer, it may occur in new locations within or outside the pelvic cavity. The carcinoma has usually been limited to the uterus at the time of hysterectomy and it may be of any histological type. The term "recurrence," although inaccurate, is used to express the concept of "reactivation of residual latent carcinoma."

The time of persistence or recurrence is shown in Fig. 1. Twenty-one cases (42 per cent) occurred within 6 months after treatment; 28 (56 per cent) within 1 year; 34 (69 per cent) within 2 years, and 42 (85 per cent) appeared within 3 years. Only 7 (15 per cent) appeared after 3 years of observation. Five (10 per cent) developed more than 5 years after treatment. This coincides closely with the observation of Speert¹ that half of the recurrences of endometrial carcinoma at the Roosevelt Hospital, New York City, were noted within the first year of treatment and that three-fourths were evident within the first 2 years. Speert, however, did not distinguish recurrence from persistence and progression of the carcinoma.

Persistent progression of carcinoma usually manifested itself within the first year after treatment. Twenty-eight patients (14 per cent) had extension of carcinoma during the first year after treatment; 11 of these (5.5 per cent) showed progression, while 17 (8.5 per cent) showed recurrence. Five

showed recurrence in the second year (3.5 per cent) while 8 (8 per cent) had recurrence during the third year after treatment. Thereafter the annual recurrence rate was about 1 per cent. Even after the conventional 5-year period of survival, 5 (6.6 per cent) of the 74 patients who were followed for more than 5 years developed recurrences. These appeared at 5, 5½, 7, 10, and 11 years. These and similar observations show exceptions to the 5-year criterion of survival. From our limited figures it would seem possible to employ 3 years as a criterion of relative safety with the realization that a 1 per cent annual recurrence rate will occur during the subsequent years after treatment. This further indicates the need for frequent examinations during the remainder of the patient's life.

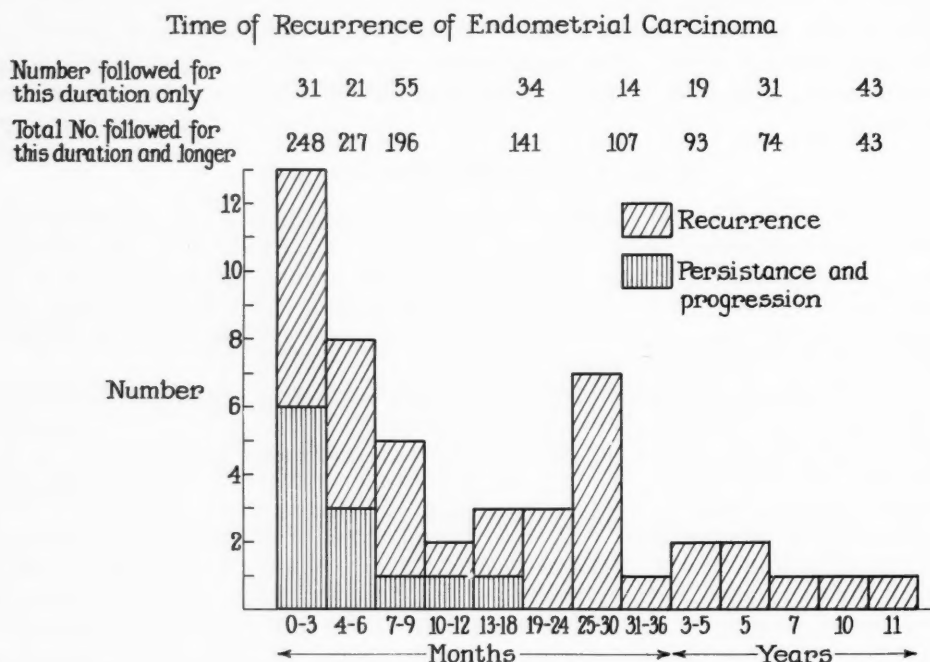


Fig. 1.—The time distribution of recurrences of endometrial carcinoma.

Factors in Recurrence

The influence of 3 factors will be considered. These are: treatment, the anatomical extent of carcinoma, and the histological grade of carcinoma. There are many other variables which may exert an important effect on recurrences. These include age, race, parity, the duration of symptoms, the presence of myomas, and estrogen therapy. These factors are not included because of difficulties in assessing their influence.

The number, the percentage, and the average time of recurrence on the basis of treatment are outlined in Table I. Five types of treatment were employed: (1) hysterectomy alone, (2) preoperative radium and hysterectomy, (3) hysterectomy and postoperative x-ray irradiation, (4) radium and x-ray irradiation alone, and (5) palliative treatment. The basic treatment at the New York Hospital is surgical. Every patient who does not present restrictive contraindications is treated by hysterectomy. This was formerly preceded by radium insertion, but the presence of residual carcinoma in 75 per cent

of the patients so treated has led to the virtual abandonment of this procedure. X-ray irradiation is usually administered postoperatively, if the carcinoma has extended beyond the endometrial cavity or has a high histological grade of malignancy. Preoperative x-ray irradiation has not been used. Combined x-ray and radium irradiation is the sole method of treatment when absolute surgical or medical contraindications to operation exist. The number of such instances is decreasing with the improvement of surgical technique and surgical adjuncts such as anesthesia, chemotherapy, and transfusion.

TABLE I. INFLUENCE OF TREATMENT OF ENDOMETRIAL CARCINOMA ON RECURRENCE

TYPE OF TREATMENT	NUMBER	RECURRENCE	%	AVERAGE TIME FROM TREATMENT TO RECURRENCE (YEARS)
1. Hysterectomy	111	10	9	2.3
2. Preoperative radium and hysterectomy	37	9	25	1.2
3. Hysterectomy and postoperative irradiation	73	18	25	1.3
4. Irradiation only	31	9	29	2.0
5. No treatment	14	3	25	0.3
Total	266	49		

The lowest recurrence rate occurred when the treatment was hysterectomy alone. This, however, does not indicate the superiority of hysterectomy alone as a mode of treatment, but merely confirms the fact that the most favorable carcinomas of low histological malignancy and of limited anatomical extent were so treated. The recurrence rates after all other types of treatment were virtually the same, 25, 25, and 29 per cent, and were approximately 3 times as high as when the treatment was hysterectomy alone. Eleven of the 14 patients in Group V refused treatment, transferred to other hospitals, or were otherwise lost to follow-up after confirmation of the diagnosis by curettage. Hence, the apparent paradox of only 3, or 25 per cent, showing recurrence of the disease while actually all 3, or 100 per cent of those who were followed, showed progression. The average time of recurrence was longer after hysterectomy alone than when hysterectomy was combined with preoperative radium or postoperative x-ray.

A clinicopathological classification of endometrial carcinoma has been described elsewhere.² There are 5 stages based on the degree of anatomical extension. Stage I includes carcinoma which is confined to the endometrium, Stage II shows penetration of the superficial myometrium, Stage III has penetration of the deep myometrium, Stage IV exhibits involvement of the tube or ovary or pelvic lymph nodes, while Stage V exhibits involvement of bladder, rectum, or extrapelvic organs or nodes. There is a direct correlation between the incidence of recurrence and the anatomical stage of the carcinoma as shown in Table II. There is a similar direct correlation between the average time of recurrence and the anatomical stage of the carcinoma. Even the lower stages of extent showed recurrence. This was about 9 per cent. Eleven of the 29 patients in Stage V transferred elsewhere, refused treatment, or were otherwise lost to follow-up, hence the paradox that only 18 (62 per cent) showed recurrence. This actually, however, represents 100 per cent of those followed. Recurrence or progression in Stage V was detected by the appearance of carcinoma in new sites such as the lungs.

The clinicopathological classification of endometrial carcinoma referred to above is also based on the histological grade. There are 3 grades: A. differentiated, B. intermediate, and C. undifferentiated. Table III shows a direct relationship between the incidence of recurrence and the histological

grade. There is a similar direct correlation between the average time of recurrence and the histological grade. Undifferentiated cancers had a recurrence rate which was 5 times as high as the differentiated carcinomas.

TABLE II. INFLUENCE OF ANATOMICAL EXTENT OF ENDOMETRIAL CARCINOMA ON RECURRENCE

EXTENT	NUMBER	RECURRENCE	%	AVERAGE TIME FROM TREATMENT TO RECURRENCE (YEARS)
1. Confined to endometrium	111	10	9	2.2
2. Penetration of superficial myometrium	59	5	8.5	3.6
3. Penetration of deep myometrium	29	8	27	1.7
4. Involvement of pelvic organs or nodes	38	8	21	1.1
5. Extrapelvic involvement	29	18	62	0.5
Total	266	49		

TABLE III. INFLUENCE OF HISTOLOGICAL GRADE OF ENDOMETRIAL CARCINOMA ON RECURRENCE

GRADE	NUMBER	RECURRENCE	%	AVERAGE TIME FROM TREATMENT TO RECURRENCE (YEARS)
A. Differentiated	153	12	8	2.3
B. Intermediate	52	10	20	2.3
C. Undifferentiated	61	27	44	1.0
Total	266	49		

In general, early carcinomas showed a low incidence and a late appearance of recurrence. The advanced carcinomas had a high incidence and an early time of recurrence.

Anatomical Sites of Recurrence

The most common sites were the remaining pelvic organs, the vagina, the bladder, the ureters, the pelvic lymph nodes, and the pelvic peritoneum, as shown in Table IV. These sites were determined by physical examination, diagnostic x-ray, reoperation, or autopsy.

The same anatomical distribution of recurrences was present regardless of the treatment, the anatomical extent, or the histological grade. The number of recurrences by site was twice as frequent when the carcinoma had penetrated beyond the serosa of the uterus (Stages IV and V) as when the carcinoma was confined within the serosa (Stages I, II, and III), although only 67 patients (25 per cent) were in Stages IV and V. Similarly, the number of recurrences by site were twice as frequent when the carcinoma was undifferentiated (Grade C) as when the carcinoma was better differentiated (Grades A and B), though the undifferentiated cancers numbered only 61, or approximately 23 per cent of the entire group.

The vast majority of recurrences were local. The most common site was the vaginal vault (Fig. 2). Fourteen recurrences developed in the vagina, 11 in the vault, and 3 in the lower vagina. Recurrences in this location have been attributed to spill at the time of hysterectomy. Such a theory does not adequately explain the late appearance of recurrences at 5, 7, and 11 years, as in 3 of these cases. Carcinoma cells have been demonstrated in the lymphatics of the upper vagina when metastases appeared lower in the vagina in 2 of our patients. The submucosal location of these metastases, their occasional late appearance, and the presence of carcinoma cells in the vaginal lymphatics favors lymphatic extension as a more adequate explanation of vaginal recurrences. This indicates the need for a more extensive removal of the upper vagina at the time of hysterectomy. The resultant shortening of the vagina does not constitute a valid objection to this procedure.

A possible measure used to prevent vaginal recurrences has been the administration of postoperative irradiation by intravaginal routes as well as by lower abdominal ports. The factors for intravaginal irradiation are low voltage, 100 to 140 kv., 5 Ma., 35 cm. skin target distance, and 1.0 mm. aluminum filtration. This very superficial irradiation is directed to 1 or 2 ports in the upper vagina by means of vaginal applicators. Its use is too recent to be evaluated.

TABLE IV. ANATOMICAL SITES OF RECURRENCE OF ENDOMETRIAL CARCINOMA

1. Genital		35
Vagina	14	
Pelvic cavity	11	
Ovary	3	
Rectovaginal septum	3	
Cervix	2	
Vulva	1	
Clitoris	1	
2. Urinary		12
Ureter	7	
Bladder	4	
Urethra	1	
3. Lymph nodes		10
Iliac	2	
Aortic	2	
Inguinal	2	
Clavicular	3	
Mediastinal	1	
4. Abdominal		19
Peritoneum	7	
Omentum	3	
Bowel	3	
Liver	4	
Diaphragm	1	
Adrenal	1	
5. Pulmonary		15
Lungs	11	
Pleura	4	
6. Bone		6
Vertebrae	4	
Rib	1	
Cuboid and metatarsals	1	
7. Surface		5
Abdominal wall	4	
Breast	1	
Total		102

The high incidence of recurrent carcinoma in the pelvic cavity (Table IV) in the immediate vicinity of the extirpated uterus, about the bladder and near the uterus, suggests the necessity for wider excision. A more extensive parametrial dissection might remove microscopic extensions of carcinoma which later would appear as recurrences.

Unsuspected carcinoma of the endometrium was discovered after subtotal hysterectomy had been performed in 4 patients. Since serial sections of the lower uterus did not show carcinoma, none of the cervixes were removed. Two cervixes subsequently developed recurrence, while the other 2 did not. This experience indicates the desirability of removing the cervix if an unsuspected carcinoma of the endometrium is found after subtotal hysterectomy has been done.

The detection of carcinoma in the lymph nodes at the time of hysterectomy portended a poor prognosis. The intimate association of myometrial lymphatics, as demonstrated by Henriksen,³ permits metastasis through any lymphatic channel which drains the uterus, regardless of the location of the

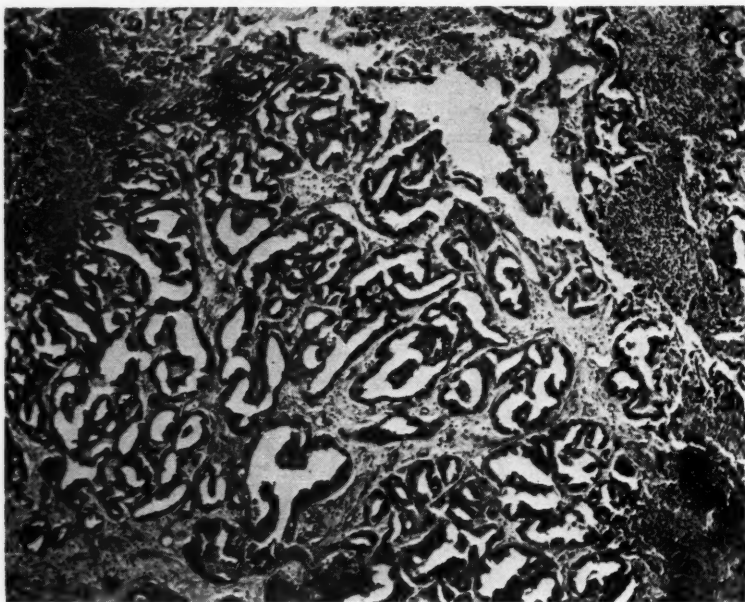


Fig. 2.—Biopsy of vaginal vault showing metastatic adenocarcinoma of the endometrium. (×30.)

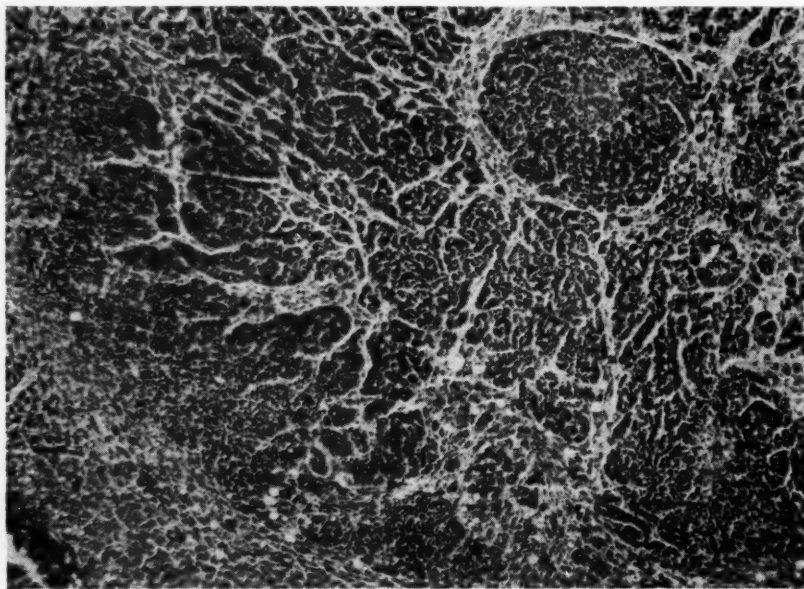


Fig. 3.—Liver with nodule of metastatic adenocarcinoma of endometrium. (×30.)

carcinoma within the endometrial cavity. Our experience with lymph node dissections in cancer of the endometrium is limited. The nodes are palpated at operation. If nodes are enlarged, they are removed for diagnostic purposes. Many enlarged nodes show hyperplasia, but no carcinoma. Thus far it has

been felt that since most endometrial carcinomas are confined to the uterus at the time of initial treatment the complications from complete pelvic lymph node dissections with exposure of the ureters would outweigh any increase in salvage in the occasional patient with lymph node extension. However, if pelvic nodes were positive and no extrapelvic sites of cancer were present, a radical hysterectomy and pelvic lymph node dissection might result in cure.

Pulmonary and bone metastases are shown in Figs. 3 and 4.

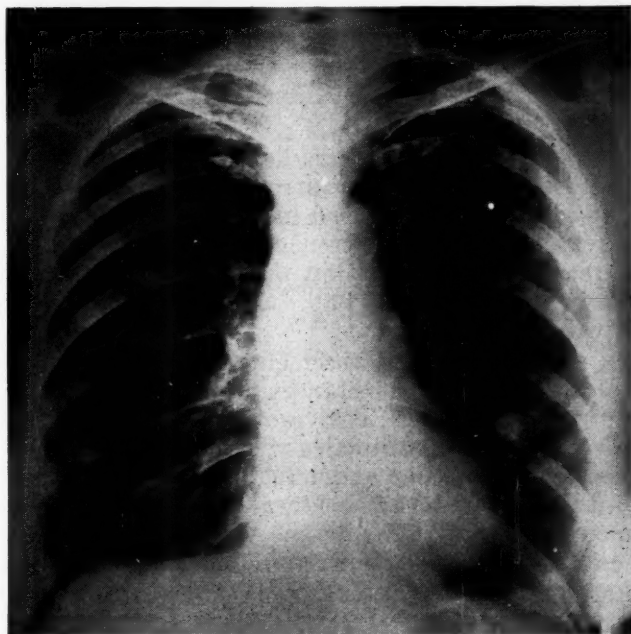


Fig. 4.—Metastases left lower lobe of lung from adenocarcinoma of the endometrium.

Detection of Recurrences

All patients are followed in a special clinic where they are seen at frequent intervals. This clinic is conducted on the principle that every patient has a potential recurrence and that it is the function of the gynecologist to detect this recurrence while it is still in a treatable stage. The patients are questioned regarding symptoms such as bleeding, abdominal or back pain, hematuria, and constipation. Careful pelvic examination is performed to detect genital or urinary tract recurrences. The abdomen is carefully palpated to detect intra-abdominal and abdominal wall masses. Biopsies of the vaginal vault, x-rays of the lumbosacral spine, cystoscopy and proctoscopy are performed as indicated. When there is doubt, the patient is admitted for examination under anesthesia. Cytological smears have not been necessary because any local recurrences which might shed cells are readily detected by inspection.

Treatment of Recurrences

Treatment is determined by the location, extent, and number of recurrences. Table V shows that 27 patients had advanced pelvic extension (15) or extrapelvic metastases (12) which precluded further irradiation or surgery. Five of the extrapelvic metastases were in the lungs, 5 in the bones, 1 in the liver, and 1 in the breast. The average time of survival of these 27 patients who received only palliative treatment was 5 months.

TABLE V. TREATMENT AND SURVIVAL AFTER RECURRENCE OF ENDOMETRIAL CARCINOMA

TREATMENT	NUMBER	SURVIVAL
None	27	0
Irradiation	9	0
Surgical	13	7
Nephrostomy	2	0
Exploratory laparotomy	3	0
Vulvectomy and vaginectomy	1	0
Completion operations	3	3
Vaginectomy	1	1
Vaginectomy, cystectomy	2	2
(transplantation ureters)		
Midcalf amputation	1	1

Nine patients were treated by irradiation. Radium was inserted intravaginally in 2 patients with vault recurrences. Both died within 2 years of treatment. X-ray irradiation was used in 7 patients. Three of these had recurrences in the vagina, 2 had recurrences in both the vagina and the pelvic cavity, 1 had a recurrent lesion within the pelvis, while the last had a subcutaneous nodule in the abdominal wall. All of these patients died, the average time of survival being 1½ years.

Surgery was employed in the treatment of 13 patients. This was merely palliative or exploratory in some instances, but was completely extirpative in the others. Two patients with extensive obstructive periureteral recurrences had nephrostomies. Three laparotomies were performed, only to reveal such widespread recurrent pelvic and abdominal carcinoma that its removal was impossible. A sixth patient had been treated by total hysterectomy and bilateral salpingo-oophorectomy. While she was receiving postoperative x-ray irradiation an extensive vulvar recurrence appeared. Vulvectomy and vaginectomy were performed, but the development of sacral metastases prevented further treatment. The patient died 2 months later.

Three other patients were treated by what may be termed "completion" operations. Two of these patients required the removal of tubes and ovaries which had been left at the time of hysterectomy, while the cervical stump was removed in another patient who had had a subtotal hysterectomy.

The remaining 4 patients had complete extirpation of localized recurrences. Vaginectomy was performed in one patient who had a recurrence in the vault after hysterectomy elsewhere. She has survived 1½ years without evident disease. The eleventh patient developed a recurrence in the vault of the vagina and at the base of the bladder 7 years after hysterectomy. The patient has survived for 2 years after vaginectomy, cystectomy, and ureterocolic transplantation. A twelfth patient developed a periurethral recurrence 2¾ years after surgery. She is now well 8 months after vaginectomy, cystectomy, and ureterocolic transplantation. The last patient is remarkable because of the unusual site of recurrence in the right cuboid and the fourth and fifth metatarsal bones (Fig. 5). Two months after hysterectomy the diagnosis of recurrence in the right ankle was confirmed by x-ray and aspiration biopsy. After x-ray irradiation had been administered without effect a midcalf amputation was performed. This patient is alive and free from metastases 6½ years later.

The survival time of those who have been treated by extensive surgery is short because this type of approach has been employed only recently. It is still too early to evaluate this trend toward surgery, but it appears to be of promise in those patients with localized solitary recurrences.

The 5 recurrences which appeared after 5 years of observation deserve special note.

CASE 1.—This 61-year-old woman with well-differentiated carcinoma confined to the endometrium (Stage I, Grade A) was treated only by 3,600 mg. hr. of exposure to radium because of severe coronary occlusion. Five years later vaginal and intrapelvic recurrences developed. Radium was again applied locally. Death occurred 1½ years later, 6½ years after the initial treatment.

CASE 2.—This 78-year-old obese woman with hypertensive cardiovascular disease was treated by subtotal hysterectomy and bilateral salpingo-oophorectomy for well-differentiated endometrial carcinoma with penetration as far as the deep myometrium (Stage III, Grade A). Serial sections of the lower uterus showed no extension, but 5½ years later a local recurrence in the cervix was treated by cervical amputation. The patient lived for 2 more years only to die of congestive heart failure without residual carcinoma 7½ years after her initial treatment.

CASE 3.—This 62-year-old patient who had been treated by total hysterectomy and bilateral salpingo-oophorectomy for a carcinoma of intermediate differentiation with penetration of the superficial myometrium (Stage II, Grade B) 7 years previously, showed recurrences in the vaginal vault and at the base of the bladder. She is still living 2 years after vaginectomy, cystectomy, and ureterocolic transplantation.

CASE 4.—A 24-year-old patient had repeated curettages because of the difficulty in making an unequivocal diagnosis of adenocarcinoma of the endometrium in this very young woman. Ten years later ovarian metastases were found at the time of hysterectomy. She is still alive 2½ years after this procedure was performed.

CASE 5.—This 55-year-old patient was treated surgically for undifferentiated carcinoma of the endometrium which had penetrated into the superficial myometrium (Stage II, Grade C). Eleven years later extensive intrapelvic involvement including the vaginal vault and the rectovaginal septum was discovered. This was before the employment of radical surgery. Death followed in 4 months.



Fig. 5.—Osteolytic metastasis from adenocarcinoma of the endometrium to right cuboid and metatarsal bones.

Summary

Forty-nine (18.4 per cent) of the 266 women with carcinoma of the endometrium who were treated at the Woman's Clinic of the New York Hospital from 1933 to 1949 showed progression of the carcinoma. Twelve (4.4 per cent) had persistence of carcinoma, while 37 (14 per cent) had true recurrences. Forty-two (85 per cent) had recurrences within 3 years of the initial treat-

ment. Seven (15 per cent) had recurrences after 3 years of observation, while 5 (10 per cent) had recurrences later than 5 years after treatment. These recurrences, well beyond the conventional 5-year period of "cure," cast doubt on this criterion of survival. A more accurate criterion might be the establishment of 3 years as a period of relative safety, with the expectation of 1 per cent annual recurrence rate thereafter. The recurrence rate was 9 per cent when the treatment was hysterectomy alone. The rate after all other forms of treatment ranged between 25 and 29 per cent. The recurrence rate was directly proportional to the anatomical extent of the carcinoma at the time of treatment. It was 6 times as frequent when the carcinoma had extended beyond the pelvic cavity (Stage V) as when it was confined to the endometrium (Stage I).

The rate of recurrence was also directly proportional to the histological grade of the carcinoma and was 5 times as common after undifferentiated cancers (Grade C) as after well-differentiated cancers (Grade A). The most common sites of recurrences were the remaining pelvic organs, the vagina, the bladder, the ureters, the pelvic lymph nodes, and the pelvic peritoneum.

Treatment of the recurrences was merely palliative in 27 patients because of their local extent or extrapelvic manifestations. Survival after recurrence in this group averaged 5 months. X-ray and radium irradiation were used to treat vaginal and intrapelvic recurrences in 9 patients. All of these patients have died. The average time of survival was 1½ years. Surgical treatment was used in 13 patients. This was palliative in 6 and definitive in 7 with localized and solitary recurrences. Six of these 7 are alive and apparently free of recurrence for an average time of 1½ years since the treatment of the recurrence.

Conclusions

1. The incidence of recurrence of endometrial carcinoma is high during the first 3 years after treatment, but thereafter approximates 1 per cent annually.

2. Cancers of lesser anatomical extent and of lower histological grade recur less frequently and at a later time than cancers of greater anatomical extent and of higher histological grade.

3. A more extensive hysterectomy with wider parametrial excision, more vaginal extirpation, and occasionally with pelvic lymph node dissection, would lower the recurrence rate. X-ray irradiation of low voltage by means of an intravaginal cone may decrease the number of vaginal recurrences.

4. Follow-up should be frequent enough to detect recurrences in a treatable form.

5. No recurrences have been cured by x-ray or radium irradiation. Extensive pelvic surgery for solitary, localized recurrences has shown encouraging results, even though the number of patients so treated is very small.

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CONSTITUTIONAL PSYCHOLOGY AND THE REPRODUCTIVE SYSTEM IN WOMEN*

A Preliminary Report

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ENVIRONMENT and heredity are the determining factors in the life of all organisms. The influence of the surroundings upon women has been the subject of two outstanding presidential addresses. In 1944, G. W. Kosmak¹ described the changes which emancipation, industrial development, war, etc., created in women and their world. In 1945, W. R. Cooke² in an address on "The Differential Psychology of the American Woman," discussed the relationship of women to their immediate surroundings, to their parents, husbands, children, and to each other under various circumstances.

Inspired by these most illuminating papers, I felt it desirable to describe the other side of the story: the influence of heredity in the life of woman. As inherited we have to consider the constitution in its broadest sense, that is, the congenital physical and mental make-up. As gynecologists, of course, we have to limit our observations to the relationship between general constitutional factors and the special female function, that of reproduction, in all its physiologic and psychologic aspects.

Even with this limitation, I am aware of the fact that we are entering a vast territory which, to cover completely, would require a lifetime. As a beginning, we have to be satisfied to point out a few outstanding landmarks in the following preliminary report.

The basis from which we start is the fact that with every type of physique there goes a definite type of temperament and character.

For thousands of years doctors as well as laymen, artists as well as poets, have felt the close relationship between the visible appearance of a person and the invisible character. Mind and body form a unit, influencing each other. In the field of pathology a large variety of observations led to what is now called psychosomatic medicine. In the field of physiology, however, which actually is the foundation of psychosomatic deviations, scientific observations have been comparatively scant. These never became very popular among practicing physicians.

The history of constitutional physiology begins with Hippocrates and his description of the "phthisic habitus" and the "apoplectic habitus." Many centuries later, about 1800, the French School (Gall and Spurzheim,³ Rostan,⁴ and others) established three main types of physical constitution: the *type digestif*, the *type musculaire*, and the *type cérébral*.

*Read at the annual meeting of the Texas Association of Obstetricians and Gynecologists, Feb. 3, 1950, San Antonio, Texas.

Later, in 1900, the Italian School (di Giovanni⁵ and Viola⁶) by using anthropometric measurements differentiated three morphologic types (micro-splanchnic, normosplanchnic, and macrosplanchnic).

An entirely new approach came from Germany in 1921. Ernst Kretschmer,⁷ professor of psychiatry, based his work of "physique and character" upon studies on the mentally ill. He arrived at three main physical types among the normal population which he named pyknic (compact), asthenic, and athletic.

Finally, in 1940 and 1942, the Americans entered the field under the leadership of W. H. Sheldon and his co-workers. They introduced the term "constitutional psychology" and gave us with their *Varieties of Human Physique*⁸ and *Varieties of Temperament*⁹ a foundation, which not only physicians and psychologists but sociologists, educators, and even theologians should utilize.

Sheldon used also anthropometric measurements and arrived at three main groups which roughly correspond with those of Kretschmer. He points out, however, that only a small percentage of people can be classified clearly (12 per cent athletic, 9 per cent asthenic, 7 per cent pyknic), and that 72 per cent appear to be mixtures. For this reason he avoids the term "type" and replaces it by the term "component." Most individuals represent mixtures of the leading three components, which are present in various degrees. These can be determined by measurements and expressed in figures. Responsible for the morphologic varieties are the germinal layers. Derivates of these three layers are not developed uniformly. Prevalence of ectoderm derivates makes an individual an "ectomorph." Prevalence of mesoderm derivates makes an individual a "mesomorph." Prevalence of endoderm derivates makes an individual an "endomorph."

For the psychologic aspect of these three components Sheldon introduces corresponding terms. Ectomorphs with their predominance of the higher centers of the nervous system are named cerebrotonic. Mesomorphs with their predominance of somatic structures are called somatotonic. Endomorphs with their predominance of the viscera are called viscerotonic.

Kretschmer's work on *Physique and Character*, published in 1921, was an inspiration to me in my daily work and contacts. Again and again among my friends, associates, and patients I found his types verified to an amazing degree. Even if it has to be stressed that the pure types are rare and that most people are a blend of various types, it is also true that one type will prevail over the others in any given person.

Entering the field of gynecology and obstetrics some twenty-eight years ago, I made it a habit to classify my patients and to observe traits in my specialty which seem to recur frequently in each group. These gynecologic observations were subdivided into morphologic, physiologic, and psychologic. A clarification of many details along morphologic as well as psychologic lines came with the publications of Sheldon^{8, 9} which I recommend highly to anybody interested in these problems.

That the reproductive system might reflect the varieties of physique and temperament is not surprising, when we consider the central position of the endocrine glands and their influence on sexual development and behavior.

Within this brief essay I shall endeavor to present the three basic groups and add what I found typical for each variety in the gynecologic-obstetric field.

A. The Endomorph-Pyknic Group

This group is found much more frequently in women than in men, according to Sheldon's figures.^{8, 9}

1. *Physical characteristics:* Short, stocky figure because of short gracile extremities. Predominance of trunk over extremities. Predominance of abdomen over thorax. Short neck. Large round head. Face broader around chin than forehead. Short stubby nose. Broad mouth with soft, full lips. Smooth contours throughout the body. Small soft hands and feet. Skin smooth and soft. Tendency to fat accumulation in later years.

2. *General psychologic traits (viscerotonic-cyclothymic):* Extrovert, emotional, good-natured, usually happy, sometimes sad, easily changing from one mood to another, in pathologic cases manic-depressive. Good mixers and sociable, warm-hearted and sympathetic, sense of humor. Love of comfort and relaxation. Love of eating. Greed for affection and approval. Few inhibitions. These people "do not know strangers," they are tolerant, and "keep their feet on the ground." They usually are at ease, optimistic, and at peace with the world and themselves. The "heart" dominates the "brain." They are not very ambitious. When in trouble they need other people.

3. *Female sex characteristics:*

a. *Anatomic:* Full hair on head. No hirsutism on face, chest, abdomen, or extremities. Feminine type of escutcheon. Vulva and vagina fully developed. Uterus and adnexa fully mature.

b. *Physiologic:* Early onset of menstrual function. Periods regular. No dysmenorrhea. Normal libido and good sexual response. Good fertility, normal pregnancies, normal labors, and easy deliveries. Good lactation. Endocrine picture fully feminine.

c. *Special psychologic traits:* These women make good wives and mothers, are good cooks and hostesses. They have strong natural instincts and enjoy life. They are not glamour girls and not career women, but they are the "salt of the earth." They like people and people like them. They are frank, but carry no grudges, like to laugh, and love a good cry. They are loyal and cooperative. Kitchen, home, and family are their world. They do not think much of "high brow activities," but tolerate them and participate in them good naturedly. They make good and grateful patients.

B. The Mesomorph-Athletic Group

1. *Physical characteristics:* Usually tall figures. Large prominent bones. Broad shoulders. Thoracic volume predominant over abdominal volume. Heavy muscular arms and legs, big hands and feet, bony long face, heavy supraorbital ridges, square jaw, strong neck, low waist on account of long thorax. Skin thick and coarse.

2. *General psychologic traits (somatotonic):* Extrovert. Matter-of-fact attitude. Better balanced, but less warm-hearted than the pyknic group. Ready to take the lead and to take responsibilities. Energetic, sometimes aggressive. Directness of manner. Physical courage. Love for exercise and outdoor activities. Claustrophobia. Manual work preferred to book work. Frequently intelligent, but not intellectual. Prefer adventure and danger to comfort and relaxation. Love a good fight. Reliable comrade to friends. Indifference to pain. Unrestrained voice, forceful movements. Very ambitious, even ruthless toward competitors. When in trouble, they need action.

3. *Female sex characteristics:*

This group is found less frequently in women than in men.

a. *Anatomic:* Hair usually feminine, occasionally male type of hirsutism with hair around nipples, on thighs, abdominal midline, etc. Breasts are medium sized or small. Hips and pelvis medium sized or android. Pelvic organs normal or hypodeveloped in accordance with general endocrine picture.

b. Physiologic: Appearance of menarche at normal age or delayed. Menstruation regular or irregular according to masculine factor. Fertility and course of pregnancy not as reliable as in the pyknic group. Labor and delivery according to pelvic features. In android pelvises sometimes slow labor, malpositions, and difficult deliveries. Sexual desire not very outspoken. Endocrine tendency toward masculinity.

c. Special psychologic traits: Somatotonic-athletic women are less feminine than the pyknic group. They are often somewhat masculine. They are cool natured. They are hard workers and good organizers in household and any type of job. They are not the romantic type, but dependable. They consider their task as wives and mothers more as a duty than a pleasure, but will stick to it faithfully. They are thrifty and not interested in luxuries. They "wear the pants." They are more respected than loved. They keep their heads up under adverse circumstances. They are at their best when action is needed. They are well suited for rural surroundings. As patients they do not like to be pampered. They can "take a lot," but are rather independent.

C. The Ectomorph-Asthenic Group

1. Physical characteristics: Long slender figure, trunk relatively short because of long extremities. These individuals especially in younger years seem to be "all arms and legs." Shoulders are drooping. Thorax narrow and long in comparison to small flat abdomen. Hips slender. Weak thighs and upper arms. Long hands and feet with long fragile fingers and toes. Long, slender neck. The face is oval shaped or triangular, the upper half broader than the lower half. The cranial mass is bigger than the facial mass. The nose is prominent and the chin receding, thus producing an angled profile. The lips are thin, the mouth small, the chin pointed. Bony structures are generally thin, long, and fragile. Muscular development is poor. Skin is thin and dry. Tendency to acne in younger years. Hair is fine and thin. Tendency to low blood pressure, anemia, enteroptosis, hernias, etc.

2. General psychologic traits (cerebrotonic-schizothymic): These people are introverts. Between their inner selves and the outer world is an invisible wall. They have split personalities. What they feel and think is one thing and what they show and how they want to appear another. They are full of inhibitions. All their reactions go through some mental process which reduces spontaneity and produces artificiality, in pathologic cases schizophrenia. There are tenseness and restraint in all movements, the lips are tight, the muscles unrelaxed. There are always nervous tension and irritability. There is little sense of humor. These people are hard to please. They are critical toward others and critical toward themselves. They are selfconscious, unsocial, and ill at ease. They are unpredictable and dogmatic, impatient, apprehensive, and oversensitive. They are wide awake, suspicious, and pessimistic, never quite happy. They are the worrying kind. They dislike physical activities and outdoor life. They prefer book work to manual work. They like to withdraw into their dream world of books, music, art, travel, or sickness as an escape from realities. They have a genius for being "misunderstood." They hate to be conspicuous. When worried or in trouble, they "want to be alone."

3. Female sex characteristics:

a. Anatomic: Thin, weak hair on head, often light fuzz on upper lip, cheeks and chin. Male type escutcheon. Occasionally hirsutism on breasts, abdomen, and thighs. Breasts small and flat. Hips slender. Pelvis frequently small. External genital organs small and sketchy. Perineum shallow. Vagina short and narrow. Uterus hypoplastic, often retrodisplaced. Tubes long, thin, and winding, ovaries cystic.

b. Physiologic: Beginning of menstrual cycle in the middle or late teens. Phases of polymenorrhea, amenorrhea, and oligomenorrhea. Severe dysmenorrhea especially before marriage. Dyspareunia and frigidity. Lack of primary passion and lack of sexual gratification. Sometimes primary sterility or habitual abortions. Endometriosis. During early pregnancy, hyperemesis. Long-drawn-out labors and uterine inertia. Tendency to postpartum hemorrhage. Endocrine picture weak.

c. Special psychologic traits: The women in this group are physically inadequate and therefore never quite well. They are easily tired and nervous. They are difficult as daughters, wives, and mothers. They are poor eaters and therefore make poor cooks. They never create a completely happy home atmosphere. They might be glamour girls and sophisticated, but they are never really popular. As girls they start having dates later in life than the other groups. But when they do, it becomes usually a rather serious and steady affair.

Marriage and motherhood with its tremendous endocrine stimulus sometimes bring out the best in them. The care of household, husband, and children, however, never satisfies them completely, tires them out easily. Little things upset them. They want to be worked for, rather than working for others. In well-to-do families these women often become a burden to themselves and their families.

As patients they have to be handled extremely carefully. They are mentally and physically very sensitive, unstable and ungrateful, egotistic and demanding. This group more than any other provides the great army of frustrated and neurotic women who fill the reception rooms of doctors. Many of them are dumped into the laps of psychiatrists and psychoanalysts when they go through the menopause.

Comment

The presentation of the three leading constitutional groups will undoubtedly bring to your minds immediately individual women who fit perfectly into one or the other group. As mentioned before, the pure types are in the minority because by marriage and heredity nature reshuffles the cards again and again. The majority of women represent a mixture of these components. We actually find in many individuals morphologic, physiologic, and psychologic traits which belong to different groups.

It is for this reason that in this short preliminary report I cannot present extensive statistical material.

There are, in addition to the physiologic groups, pathologic varieties which are to a large extent connected with hyper- or hypofunction of some other endocrine gland like the thyroid, the adrenals, etc.

I would like, however, to mention one observation which I encountered and which I feel I should present in actual figures on account of its startling character. It concerns the relationship between intelligence and the reproductive system in women.

I have developed the habit of interviewing every new gynecologic patient concerning her scholastic record and background. While I found in the endomorph and mesomorph groups nothing unusual, I noticed in the prevalent ectomorph-cerebrotonic group a definite tendency to higher scholastic accomplishments.

It is in this group that we find so many women with genital hypodevelopment, dysmenorrhea, frigidity, sterility, etc.

Women with primary sterility who see the physician for this particular indication present the most outspoken picture of endocrine female insufficiency.

During the last year I interviewed 150 women with primary sterility. As indicator for their scholastic accomplishments I recorded mainly their status at high school graduation. Their subsequent scholastic career does not permit any statistical conclusions, since many of them did not continue, but had to take a job for economic reasons or got married. In these 150 women with primary sterility I found 122, or 81.7 per cent, above average. Twenty-eight, or 18.7 per cent, were average. Ninety, or 60 per cent, of the total belonged to the highest 10 per cent in their graduating classes. Thirty-two, or 21.3 per cent of the total, had a B average. There were five valedictorians and three salutatorians in this group. Many of these patients belonged to the National Honor Society, obtained scholarships, etc. Thirty-six graduated later from various colleges. Three received masters' degrees, one obtained an M.D.

The most striking fact is that 90 (60 per cent) or almost two-thirds of these women with primary sterility belonged to the highest 10 per cent of their classes when they graduated from high school. The most outstanding physical feature is their hypogonadism and hypoestrinism with all their morphologic and physiologic consequences.

I have no doubt that a certain antagonism exists between true feminism and that particular brand of intellect which manifests itself in scholastic accomplishments.

I do not want to imply that truly feminine women are less intelligent. Theirs is a different type of intelligence which expresses itself more by the way of instinct and feeling than by the way of logical deductions and scholarly thinking. Fully feminine women are closer to nature. Their main goal in life is fortunately still a successful marriage, a happy home, and children. It is the group with above-average scholastic record and below-average femininity who often do not make a success of marriage and motherhood. Needless to say, there are women who have both the scholastic brand of intellect and normal womanhood. On the other side we find women with mental as well as physical infantilism.

Summary

1. Physique and character are inherited factors of the constitution which form an inseparable unit in every type of individual.

2. Three leading constitutional groups are described according to morphologic and psychologic features. These groups are determined by prevalence of ectoderm, mesoderm, or endoderm derivatives.

3. In women each of the leading constitutional groups possesses typical anatomic and physiologic features of the reproductive system which are reflected in menstrual function, course of pregnancy, labor, delivery, etc. They are also reflected in typical psychologic reactions and behavior during adolescence, matrimony, and motherhood. The endocrine glands occupy a key position in determining the varieties.

4. An interesting light is thrown upon the relationship between cerebral activities and the reproductive system in women by the fact that in 150 women with primary sterility, caused by hypogonadism and hypoestrinism, an unexpectedly large percentage of high scholastic accomplishments could be registered. One hundred twenty-two, or 81.7 per cent, were above average, ninety, or 60 per cent, belonged to the top 10 per cent of their classes at high school graduation.

Conclusions

The knowledge of background and heredity is of great importance in handling individual patients. In former days the family physician acquired this faculty in his fingertips through his daily contacts. The modern specialist is deprived of this advantage and has to replace it by a good working knowledge of constitutional psychology. It is amazing how much information one can gather from observing morphologic traits at the very first interview. This is especially true in gynecologic practice, where simple facts are often hidden behind clouds of emotions. The analysis of every patient on the basis of physique, temperament, and intelligence not only adds color to the sometimes monotonous daily practice, it leads to better understanding and results.

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ANOVLATORY MENSTRUATION IN WOMEN

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HITSCHMANN and Adler¹ in 1908 postulated the theory that menstruation might be related to the phenomenon of ovulation, and since then the term menstruation has been used to indicate cyclic uterine bleeding of ovulatory nature. Robert Meyer² emphasized that "Ohne ovulation keine corpus luteum. Ohne corpus luteum keine menstruation," while Schroeder³ went so far as to suggest that the term "menstruation" be restricted to cases of ovulatory bleeding only and that in the absence of ovulation, cyclic bleeding should be called "pseudo-menstruation." This latter view is not shared by modern students of the subject.

In recent years there has been overwhelming evidence that cyclic bleeding of the anovulatory type can occur and that it is clinically indistinguishable from ovulatory menstruation in duration, amount, and nature. Early workers, like Heape,⁴ 1894, and Van Herwerden,⁵ 1905, first observed that wild monkeys menstruated in the absence of corpus luteum. However, E. Allen,⁶ Hartman,⁷ and Corner⁸ introduced the modern phase of this field with their work on the rhesus monkey (*Macaca mullata*). Hartman⁷ correlated the occurrence of ovulation with sex skin reaction, vaginal lavage, rectal palpation, and laparotomy. In apparently healthy animals which menstruate regularly throughout the year, he found that menstruation without the formation of a corpus luteum was the rule in the summer months while ovulatory cycles were prevalent in winter. Similar anovulatory cycles in monkeys were also common in puberty, postpartum period, lactation, and after strenuous journeys or physical illness, probably explaining the relative infertility during these periods.

Corner,⁸ 1923 and 1927, in addition to his excellent work on the rhesus monkeys, deserves the credit of calling to our attention a similar phenomenon in the human female. Novak,⁹ 1930, in appraising the value of endometrial biopsy as the most practical available means of indirectly detecting ovulation, suggested that anovulation was not uncommon in women as a cause of unexplained sterility. In 1941 he was able to collect thirty-nine such patients, of whom the diagnosis was made by endometrial biopsy in only nineteen.

Mazer, Israel, and Kacher¹⁰ believed that the appearance of the endometrium was not an absolute proof of ovulation, since there were instances in which an inherent lack of response was the cause of the endometrium being refractory to the ovarian hormone incited by ovulation. These workers revived the terminology pseudo-menstruation, used by Schroeder, for cases in which the diagnosis of anovulation was made by endometrial biopsy only.

Incidence of Anovulatory Cycles

There is much discrepancy between figures presented by different workers on the incidence of anovulatory cycles in various groups of women. It is now apparent that in many instances doubtful diagnostic methods or interpretations were used. Earlier observers, like Mazer and Ziserman¹¹ claimed as much as 50 per cent of forty sterile women with normal menstrual history had non-secretory endometrium at the time of investigation. Later Mazer and Israel¹⁰ were able to reduce this figure to 30 per cent. Jeffcoate,¹² the first English author to report on the possibility of anovulatory cycles in women, reported 16 out of 63 endometrial biopsies, or 1 in 4, which showed absence of progestational activity in the premenstrual phase. Rock, Bartlett, and Matson¹³ employed the endometrial biopsy method on a large scale in 392 sterile women and were able to find 36 patients (9.1 per cent) showing anovulatory endometrium taken within ten days before the onset of the succeeding menstrual period. Since then other published data showed no striking difference from the data of Rock et al. (Sharman,¹⁴ 6.4 per cent; Sevvitt,¹⁵ 10 per cent; Cross,¹⁶ 5.1-8 per cent; Johnstone,¹⁷ 4.7 per cent; Levan and Santo,¹⁸ 5.36 per cent. The last-mentioned series, however, was taken from institutionalized patients in whom the incidence of amenorrhea, infertility, and failure of ovulation might be expected to be higher than normal.)

It is now clear that anovulation is more often sporadic than permanent and that a perfect progestational picture of the endometrium in one cycle does not exclude the possibility of anovulation in another. It is also possible that the true incidence of anovulation among the female population is much higher than figures presented to date. Methods for the precise detection of ovulation have not yet been perfected. Numerous proposals of such methods have been made, few of which have withstood the test of time.

Numerous observers have attempted to show the correlation of pituitary gonadotrophin excretion with ovulation, the most recent offering being that of Farris.¹⁹ However, our experience with this test has not led to any degree of confidence in its validity (Levin, Buxton, and Engle²⁰). Assays of pregnandiol, or its sodium salt, have considerable utility. However, if single samples of urines are taken, negative reports have no value.

The basal body temperature chart, at present, has the most extensive use as a diagnostic method for determination of ovulation. Buxton and Engle²¹ have recently shown that this method, in the cases studied, is not chronologically accurate, there being a variability of as much as four to five days on occasion between the ovulatory temperature rise and actual ovulation.

This fact was determined by carrying out elective laparotomies at the time of the midcycle temperature rise. The age of the corpora lutea removed at this time, as determined microscopically, varied as much as five days. Furthermore, in a study of 127 menstrual cycles in 38 patients, 47, or 37 per cent, had such a slow or equivocal temperature rise that no conclusions could be drawn as to time of ovulation, or even if ovulation had actually occurred.

The endometrial biopsy is at present the most reliable technique available for the evaluation of the effect of endogenous or exogenous estrogen or progesterone on the uterine mucous membrane.

Material

The endometrial biopsies from a large outpatient clinic material have for more than a decade been read by one of us (E.T.E.), and recorded. Accurate dates of the preceding and the subsequent menstrual flow is essential to the interpretation of the biopsy. In this clinic, the exact dates of the preceding menstrual period are recorded at the time of the endometrial biopsy. At this

time the patient is given an addressed postcard, with instructions to record the first day of the subsequent period on the postcard and mail it to the clinic.

From these records we have drawn all cases diagnosed as anovulatory. Only those cases which meet the following criteria are presented in this report, the other records being rejected as uncertain:

1. The previous menstrual period must have preceded the biopsy by at least twenty-one days. Cases of irregular or sporadic bleeding have been excluded by our definition.

2. The biopsy in the cases reported here must be taken within two days of the next flow, as recorded by the patient at the time the period began. This rule has resulted in the exclusion of many cases with proliferative endometrium in which the flow followed the biopsy by three or four or more days. We presume that most of these cases were also anovulatory. However, cases of late ovulation, with a short secretory phase (Buxton²²) or of an inadequate progestational response (Hamblen²³) might vitiate the reliability of a diagnosis of nonovulation if more than two days elapsed after the biopsy.

3. Cases were excluded from this study if the menstrual period had started more than twelve hours previous to the biopsy. Within the first twelve hours enough glands can be seen for an accurate diagnosis of this point; later stages too frequently yield only endometrium basalis or necrotic tissue.

4. In all cases presented here the duration and degree of flow was checked so that cases of traumatic bleeding as a result of the biopsy could not be included.

5. These patients have had no previous hormone medication.

6. This series includes no adolescent girls.

Clinical Material.—This discussion is based on 36 women of childbearing age, whose complaint was involuntary sterility. These anovulatory cycles were found on routine endometrial biopsies made along with other diagnostic procedures. There were 47 instances of anovulatory cycles in these 36 patients.

The age groups were as follows: two patients were 19 years old, twenty-three were between 20 and 30, ten were between 31 and 40, and one was over 40 years of age.

The majority of these patients, 28 of the 36, were nulliparous, only 8 of the 36 having had living children. Four had one child, and two had, each, two and three children, respectively. The duration of sterility ranged from one to nine years. The spontaneous abortion history among the nulliparous patients is pertinent. Three women had one, and three others had two spontaneous abortions, while one patient had a history of three spontaneous abortions.

The menstrual history also reflected this poor reproductive performance. Slightly more than one-third of these women (13 of 36) had normal menstruation. Ten had oligomenorrhea, while seven others had oligomenorrhea followed by episodes of temporary secondary amenorrhea of some months' duration. Five additional patients had a history of normal cycles interspersed with short periods of secondary amenorrhea. A single patient had menorrhagia.

This small group of patients selected for this report because of anovulatory menstruation presented in addition a large proportion of the usual menstrual abnormalities. Anovulatory cycles are merely another manifestation of disturbed endocrine balance, so evident in this group. Indeed, anovulatory cycles may be much more frequent in this series than our data indicate, as serial biopsies were not taken on these patients.

The thyroid status of these patients will be reported elsewhere in connection with a larger series. Suffice it to say that although one-third of this group

of women showed a basal metabolic rate ranging from -10 to -30, hypothyroidism did not appear to be a contributing factor to anovulation.

TABLE I

ANOVULATORY CYCLES	PATIENTS
Single anovulatory cycle (one biopsy only)	16
Two anovulatory cycles (two biopsies)	2
Previous presumptive anovulatory cycles (biopsies taken before the last two days of cycles) followed by two proved anovulatory cycles	1
Previous ovulation followed by occasional anovulatory cycles	7
Anovulatory cycles followed by ovulation	8
Inadequate secretory cycles mixed with anovulatory cycles	2
Total	36

From Table I it is evident that the majority of patients had had more than one biopsy taken, from which the diagnosis of anovulation was made. The number of anovulating cycles in these patients ranged from one to five. Nineteen of thirty-six patients proved to be anovulatory for the entire duration of investigation and follow-up, while the remainder, seventeen, were periodically so. Pregnancy resulted in four patients in the latter group.

Other Clinical Entities.—There were thirteen patients judged to be obese, five patients with pelvic inflammatory disease, four with uterine fibromyomata, one with pelvic endometriosis, and one with a chromophilic adenoma of the pituitary, with incipient acromegaly. The over-all clinical picture of these thirty-six patients showed a fairly constant correlation between obesity, mild hirsutism, and anovulation. The relevant features of a few cases are enumerated below.

Abstract of Cases

CASE 1.—Mrs. S. L. was a 34-year-old nulliparous housewife who gave a history of oligomenorrhea and sterility. Her periods began at the age of 13; the interval was irregular, ranging from one to four months, and the flow lasted for four to seven days. When first seen she was moderately obese with a basal metabolic rate of -3 per cent and mild hirsutism.

An endometrial biopsy taken on the twenty-sixth day of a twenty-eight-day cycle showed poor, inactive endometrium. The subsequent menstrual periods were normal in duration and amount. This patient was put on a reducing diet and thyroid therapy, which produced no remarkable variation in either the basal metabolic rate or serum cholesterol. The catamenias, however, became and remained regular with cycles of approximately thirty days.

Five subsequent biopsies were taken in different cycles within one to two days of the menstrual flow, showing various degrees of proliferative endometrium, the majority of which appeared inactive. The maximal estrogenic activity in these biopsies appeared to be equivalent to the tenth or twelfth day of a normal twenty-eight-day cycle. Only in one cycle could inadequate secretory changes be found. Her basal body temperature records corresponded to the endometrial findings.

CASE 2.—Mrs. Z. B., 34 years old, was investigated for sterility. She gave a normal menstrual history and had had two spontaneous abortions under twelve weeks for which no apparent cause could be found.

On her first visit, her basal metabolic rate, serum cholesterol, protein-bound iodine and radioactive iodine uptake, among other investigations, were within normal limits. Endometrial biopsy taken on the twenty-seventh day of a twenty-nine-day cycle showed inactive proliferative endometrium with small tubular glands and no mitosis.

She was given thyroid therapy, and subsequently ovulation was proved by both basal body temperature records and endometrial biopsy. Of the thyroid function tests, only the

radioactive iodine showed a significant decrease from 24 per cent to 1 per cent in three months, as a result of thyroid therapy. This patient became pregnant after the last biopsy, which produced no ill effect on the pregnancy. She is at present five months pregnant.

CASE 3.—Mrs. G. O., an obese, 20-year-old nulliparous housewife, complained of two periods of secondary amenorrhea of three and four months' duration, respectively. Previous to that, her menstrual history was perfectly normal. Apart from her obesity nothing abnormal could be found on physical examination. Her thyroid function tests were normal. Endometrial biopsy revealed proliferative endometrium with some degree of estrogenic activity.

Fig. 1.



Fig. 2.

Fig. 1.—Active proliferative endometrium taken on thirtieth day of a thirty-two-day cycle. The nuclei of the glandular epithelium are arranged in many layers, and one mitotic figure is partially extruded into lumen. ($\times 700$.)

Fig. 2.—Active proliferative endometrium showing mitotic figure completely cast into lumen of gland. Biopsy taken on thirty-ninth day of forty-one-day cycle. ($\times 700$.)

As she was used as a control case, she was given a placebo similar in appearance and taste to thyroid tablets and put on a reducing diet. As her weight came down from 200 to 170 pounds, she began to menstruate regularly every thirty to thirty-five days. Her basal temperature records, however, remained flat; and two out of three endometrial biopsies taken one to two days premenstrually revealed active proliferative endometrium, the third showing inadequate secretory response.

Her basal metabolic rate, serum cholesterol, protein-bound iodine, and radioactive iodine tests remained constant.

The Endometrium

The histological patterns of the endometrium are quite uniformly grouped into two categories: those with indications of estrogenic stimulus, or active proliferative, and those which show no indication of estrogen activity, which are designated as inactive proliferative. Descriptions of these two types of tissue with microphotographs are given in more detail.

Fig. 3.

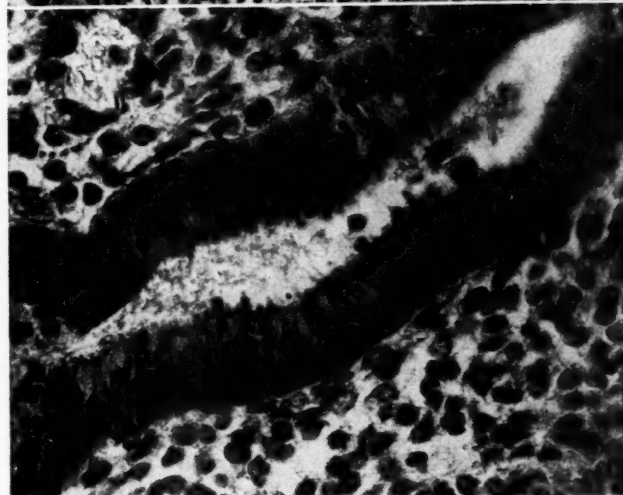
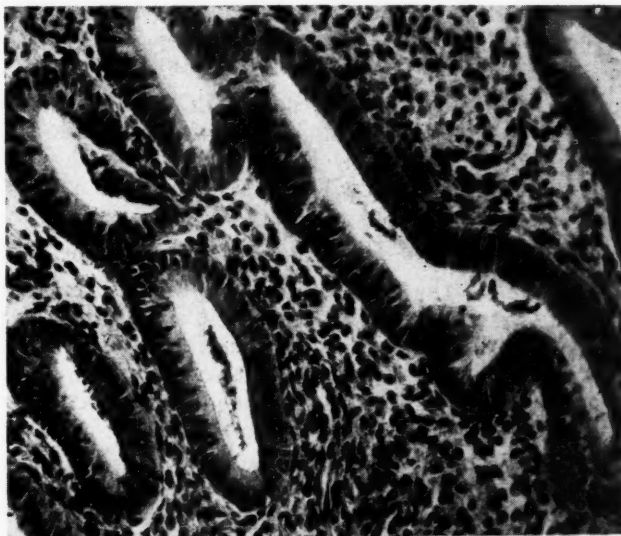


Fig. 4.

Fig. 3.—Endometrial biopsy showing darkly stained rod-shaped nuclei in the glandular epithelium similar in appearance to the "peg cells" of the Fallopian tube. ($\times 350$.)

Fig. 4.—Endometrial gland showing partial extrusion of rod-shaped nuclei into the lumen. ($\times 700$.)

Active Proliferative, Menstrual

The glands are unequal in size, many are smaller than normal. The glandular epithelium is uniform in most glands, being tall simple columnar. The apical cell membrane is intact. The nuclei are oval in shape and are densely

packed. They are located within the cells at various levels from the base to the apex of the cells. They are basophilic and highly chromatic. The nuclei at the apex of the cell are round in shape, and have a loose chromatin. Many mitotic spindles for cell division have formed in these apical nuclei. In most instances the mitotic figure shows atypical characters and the cells appear to break up without completing cell division. In some instances the entire aberrant spindle is cast into the lumen of the gland (Figs. 1 and 2). There are two cystic glands in one specimen. The major histological difference between this and normal proliferative endometrium of the preovulatory phase appears to be the atypical as contrasted to the usual normal mitotic figures.

The stroma is dense, without edema. The stromal cells have little cytoplasm and deeply staining nuclei.

The arterioles in the stroma are scant with thin walls, reduced musculature, and appear to have few coiled loops. Venous sinuses are not congested, but there is interstitial hemorrhage. The stroma is invaded with lymphocytes and polymorphonuclear leucocytes. There are no plasma cells.

Inactive Proliferative

The glands are small, the epithelium simple columnar. The nuclei are deeply staining and very densely packed. A constant characteristic of an inactive proliferative is the absence of mitotic figures. Perhaps as a result of this, many pyknotic nuclei, very thin and narrow, are being extruded from the cells. These structures are definite nuclei, seen mainly at the cell apex where they may protrude for half their length into the lumen of the gland. There is much histological resemblance between these gland cells and the so-called "peg cells" of the Fallopian tube (Figs. 3 and 4).

The stroma is compact, the cells with scant cytoplasm. The blood vessels are sparse, thin-walled, and not dilated.

The over-all histological impression is one of very limited metabolic activity. This is possibly related to a low estrogen titer.

Summary

1. Forty-seven endometrial biopsies obtained with the Meig's curette from thirty-six sterility patients proved to be anovulatory. These patients had had no previous hormone therapy, and the biopsies were taken within forty-eight hours prior to the onset of menstrual flow, so that cases of doubtful ovulation or short secretory phase were excluded.

2. The true incidence of anovulatory cycles is perhaps much higher than usually suspected. Reliable methods of investigation are not routinely available in every cycle. For this purpose the basal body temperature record appears to be the most convenient, but unfortunately this is not as reliable as the endometrial biopsy.

3. The number of anovulatory cycles in these thirty-six patients varied from one to five. Nineteen patients were anovulatory continuously while under investigation, for several months to a year; whereas, the remainder, seventeen patients (1 out of 2), were periodically so.

4. The menstrual history of these patients presented interesting features. Thirteen of these patients (one-third) had a normal menstrual history, while the rest presented history of oligomenorrhea or secondary amenorrhea. Only one patient had menorrhagia. The first group of patients were mostly sporadically anovulatory.

5. Sterility patients with a clinical picture of obesity, hirsutism, or menstrual irregularities should lead one to suspect the possibility of anovulation, since these findings are all manifestations of hormonal imbalance.

6. The endometrial picture of anovulatory cycles can be classified into two types, the active and inactive proliferative. In the former, there are aberrant mitoses, many of which are apical in position and appear to be in various stages of extrusion. In the latter group of inactive proliferative endometrium, mitoses are absent, but the so-called "peg cells" are apparently in a similar process of being extruded. This may be taken as a sign of low estrogenic activity. The coiled arterioles of the endometrium form few loops and are only seen in the deeper layer of the endometrium so that many specimens do not contain arteriolar fields at all. These arterioles are thin-walled and appear very different from their counterparts in the secretory endometrium.

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**A MORPHOLOGIC AND CYTOCHEMICAL VAGINAL-SMEAR STUDY:
THE EFFECT OF TOPICAL PENICILLIN IN THE TREATMENT OF
FOCAL INFECTIONS OF THE VAGINAL TRACT**

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WHILE investigating the absorption of penicillin from vaginal suppositories, Abel and associates,¹ and Walter and collaborators² have demonstrated that topical penicillin is of value in the treatment of vaginitis and cervicitis. However, in their studies larger doses than those required for a topical effect were used in attempts to achieve a therapeutic penicillin blood level. Accordingly, the results fail to provide a clinical guide to the rational use of penicillin in the vaginal tract as a purely topical agent. In the course of a recent study on the effects of antibiotics upon vaginal glycogen we had an opportunity to obtain information on this aspect of the clinical use of penicillin.

It has been shown by Mack³ and Rakoff and co-workers⁴ that the glycogen content of the epithelial cells in the vaginal fluid varies during the normal menstrual cycle, with maximal concentrations coinciding with periods of maximal follicular activity. This is in accord with the well-established fact that estrogen promotes the accumulation of glycogen in the vaginal epithelium. Mack³ has also observed that in the presence of focal infection in the vaginal tract the vaginal smear is glycogenic throughout the cycle, despite normal ovarian activity. He has suggested that this may result from the action of some "antihormonal" factor which presumably interferes with the accumulation of glycogen in the epithelial cell as regulated by the estrogenic stimulus. It was considered of interest to investigate further this effect of chronic focal infection upon the glycogen metabolism of the vaginal tract. As an initial approach, a number of subjects with chronic cervicitis and an associated vaginal smear glycopenia were treated with graded doses of topical penicillin to determine the effects of bacteriostasis upon the glycogen content of the cells of the vaginal fluid.

As this effect was studied it was observed that smears taken during the course of penicillin therapy contained an unusual number of cornified cells. It was decided therefore to attempt to evaluate the effect of topical penicillin upon the vaginal tract by a combined morphologic and cytochemical vaginal-smear study.

Material and Methods

The subjects of this study were a group of 14 parous women and one nullipara ranging in age from 18 to 36 years. All were observed by clinical and cytological study through a preliminary period of at least one month. Their menstrual histories were normal. Each had a chronic cervicitis with a purulent cervical discharge and a troublesome leucorrhea. Suppositories contain-

ing 100,000 units of penicillin in a cocoa-butter base were prescribed. In a small trial series, one suppository every other day had been advised. This did not appreciably influence the leucocyte content or glycogen of the vaginal fluid. Therefore, in the present series, one suppository at bedtime was prescribed. In individual cases the suppositories were used from 7 to 34 days, and in the average case from 7 to 14 days. Since the characteristics of the vaginal fluid vary with the menstrual cycle, the use of the suppositories in relation to the phase of the menstrual cycle was recorded in each instance. In the total series they were employed for variable periods in 22 menstrual cycles; in 12 instances they were used during the first half of the cycle, or the follicular phase; and in 12 instances the period in which they were used coincided with the later half of the cycle, or the luteal phase.

Vaginal smears were taken using Papanicolaou's⁵ technique. Two smears were prepared at each visit. One was fixed in ether and alcohol (equal parts ethyl ether and 95 per cent ethyl alcohol) and stained with Papanicolaou's stain⁶; the other was fixed in 95 per cent alcohol and treated with a modification of the technique employing Best's carmine.⁷

A total of 274 vaginal smears were prepared and analyzed for this report. One hundred thirty-seven were stained with Best's carmine and an equal number with Papanicolaou's stain. The total includes 108 smears taken during the period of treatment. In each case, during the preliminary period, 6 to 10 vaginal smears were taken at significant intervals in relation to the menstrual cycle. Smears were again taken immediately before treatment and at 7-day intervals while suppositories were used. In two cases smears were taken every other day while suppositories were used throughout most of one menstrual cycle.

In the interpretation of the smears the glycogen index (G.I.), the cornification index (C.I.), and the clarity of the smear as regards the presence of bacteria and leucocytes were recorded. The G.I. has been defined by Mack³ as the percentage of glycogen-positive cells in the smear. He has found a G.I. of 75 per cent or over representative of maximal follicular activity. In his study of changes during the menstrual cycle, in a limited number of subjects, the highest G.I. values occurred in the late follicular period and declining values were observed in the luteal phase. The C.I. has been defined by d'Allende⁸ as the percentage of acidophilic-staining cells in the smear. The pattern of change in the numbers of cornified cells found in smears prepared serially throughout the normal menstrual cycle has been established by Papanicolaou.⁵ Shorr⁸ has attempted a quantitative estimation of these alterations. The highest C.I. during the normal menstrual cycle is usually found at ovulation when it averages 50 to 60 per cent. In the luteal phase declining values are found. In the late luteal phase the C.I. is seldom over 30 per cent. Papanicolaou⁹ has described the smear in cervicitis as having a generally rich bacterial flora and many leucocytes. In trichomoniasis numerous atypical cornified cells are present and most epithelial cells have a small white halo about the nucleus.

Each smear was examined by two of us independently and the results subsequently compared. The G.I. was determined by scanning the slide stained with Best's carmine under low power and estimating to the nearest 10 per cent the number of glycogen-positive cells in the smear. The C.I. was similarly determined by scanning the slides stained with Papanicolaou's stain. Individual estimates by this method conformed within 10 per cent. Where a discrepancy arose the lower value was tabulated for the interpretation of results.

Results

Examination of the smears taken during the preliminary period of observation showed glycopenia to be a consistent feature in each case. The G.I. varied from 0 to 30 per cent during the cycle. The highest value of 30 per cent, in two instances, occurred during the late follicular phase of the cycle. Vaginal smears taken following the use of the suppositories for 7 days showed a G.I. of 50 per cent or over. In 10 of the 12 cases where the suppositories were used during the follicular phase of the cycle a G.I. of 60 or more was found, in 5 cases the G.I. was 70 per cent or over. In 9 of 12 instances where the use of the suppositories coincided with the luteal phase of the cycle, a G.I. of 60 or more was found, in 6 the G.I. was 70 per cent or over.

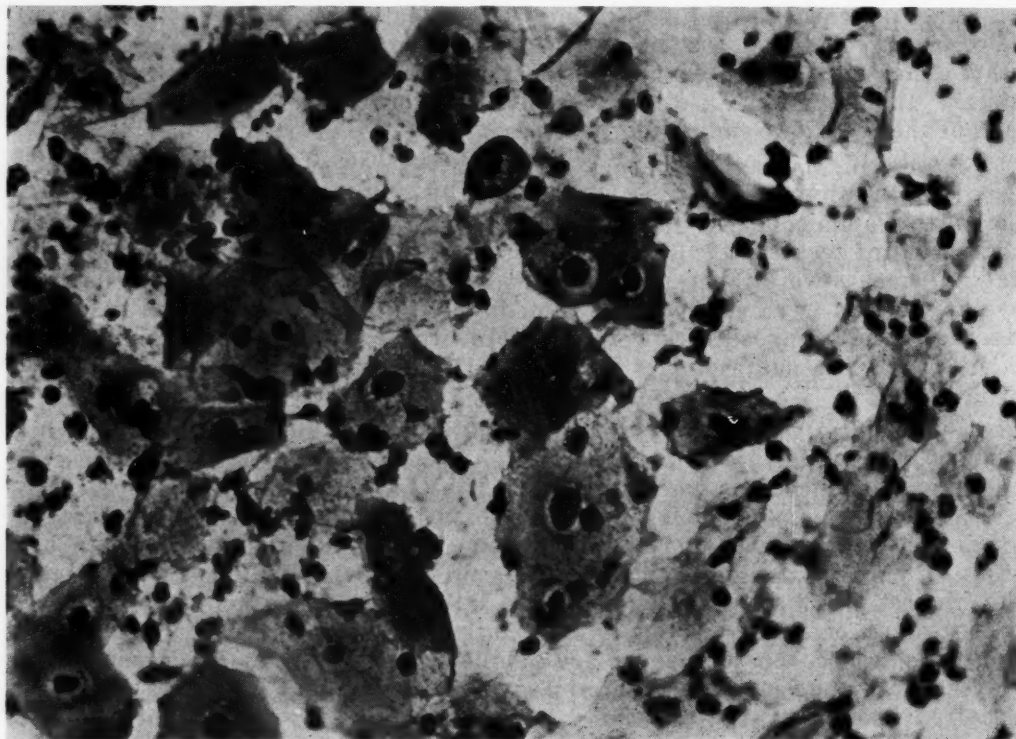


Fig. 1.—The vaginal smear picture in chronic cervicitis. Observe the indefinite borders and perinuclear halos of epithelial cells. The cells stain poorly. Mucus is abundant and contains many leucocytes, and a "heavy" mixed bacterial flora. These features are consistent throughout the menstrual cycle.

An analysis of the slides stained with Papanicolaou's stain showed that during the preliminary period there was usually a "dirty" vaginal smear picture (Fig. 1). Mucus was abundant and contained many leucocytes and visible bacteria. Trichomonads were present in 9 of the cases studied. The cells in the smear stained poorly. Their borders were irregular and indistinct. Double nucleated cells were frequently observed scattered over the slide. An ill-defined perinuclear halo was usually present. Some degree of anisonucleosis was not uncommon. The cyclic variations in the morphologic and staining characteristics of the cells followed the typical pattern described by Papanicolaou.⁵ The highest C.I. occurred during the late follicular phase but did not exceed 60 per cent. The C.I. in smears obtained during the late luteal phase was below 30 per cent. Following the use of the vaginal suppositories

in either the luteal or the follicular phase of the cycle the smear picture was usually the same (Fig. 2). Most of the cells were typical squamous epithelial cells with small pyknotic nuclei. Their cytoplasm was acidophilic. Cytoplasmic granules were frequent. Cell borders were sharp and distinct. Double nucleation was rarely observed. There were no perinuclear halos. The smear was clear in character in most instances. Neither bacteria or trichomonads were seen and leucocytes were few. The C.I. in these smears was unusually high. This was particularly notable in the luteal phase when characteristically the number of cornified cells in the smear is seldom over 30 per cent. In 9 of the 12 instances where the suppositories had been used during the follicular phase, a C.I. of 70 or over was found. In 8 of the 12 trial periods which fell in the luteal phase the C.I. was 70 or over. Values of 90 were not unusual.



Fig. 2.—The vaginal smear picture following therapy with topical penicillin. Observe clear-cut borders and absence of nuclear halos in epithelial cells. Cytoplasmic granules are frequent. Most cells are acidophilic. The smear is "clean" with a notable absence of leucocytes and visible bacteria. This picture follows the use of penicillin suppositories in both the follicular and the luteal phases of the menstrual cycle.

There were two reactions to this form of penicillin therapy. These were characterized by vaginal and vulvar itching and irritation. The cytological data in these cases is of interest. They are therefore described in detail.

CASE 1.—Mrs. M., para 1, aged 24 years, had a normal menstrual history. The use of penicillin suppositories was initiated on the first day of a 28-day cycle. A smear obtained on the fourth day was clear in character and not otherwise unusual. The C.I. was 30, the G.I. 70. A smear taken on the eleventh day of the cycle showed a C.I. of 70 and a G.I. of 80. The cells were normal in appearance. On the seventeen day the smear exhibited many atypical cornified cells. These had the appearance of large outer basal cells, but the nuclei were small and pyknotic and the cytoplasm had a hyaline texture and stained

a brilliant orange. The C.I. was 60, the G.I. 70. The patient was next seen on the twenty-fourth day of the cycle, Itching, increasing in severity, had been present for three days. The use of the suppositories had, however, been continued. On the twenty-fourth day the vaginal smear was composed entirely of basal cells which were small and round with vesicular nuclei. Anisonucleosis was a prominent feature. Almost all of the cells present contained a high concentration of glycogen. The smears throughout this series were clean and contained few leucocytes. The use of the suppositories was discontinued on the twenty-fourth day. During the following menstrual cycle the epithelial cells in the vaginal smear were normal in appearance.

CASE 2.—Mrs. A., was a 36-year-old nullipara who had been investigated for infertility. Studies over a period of four months (basal body temperatures and vaginal smears) indicated that ovulation was occurring regularly. The vaginal smear was observed to be glycopenic in character, however. Therefore a trial on penicillin suppositories was initiated. The suppositories were used daily from the fifth day of the cycle. A smear obtained on the ninth day was not unusual in character. On the fifteenth day the patient complained of vaginal itching. In the smear taken on the sixteen day many yeast bodies were found. This suggested that a yeast vaginitis had developed in the glycogen-rich environment. The epithelial cells present were of the superficial squamous type.

These two reactions were apparently of different character. The first was associated with a failure in the maturation of the cell. The second appeared to be the result of the invasion of the altered environment by a penicillin-resistant organism. In both cases symptoms disappeared within 1 to 2 days when the use of the suppositories was discontinued.

In each of the cases studied symptomatic improvement accompanied the use of the suppositories within 2 to 4 days. After 7 days' treatment, the cervix was clean, the cervical discharge was clear, mucoid in character, and not excessive in amount. In a limited number of cases smears were obtained in the cycle following that in which the suppositories had been used. The normal pattern for variations in cornified cells and glycogen content was usually found. A further follow-up study was possible after a 3-month interval in 14 of the 15 subjects studied. Eleven of this group of 14 had maintained clinical improvement, and the vaginal smears at this time were normal in character. Three had had a recurrence of symptoms and the vaginal-smear picture suggested that the inflammatory process had returned.

Comment

The results of this study demonstrate that relatively small amounts of topical penicillin will serve in the treatment of chronic cervicitis with leucorrhea. Suppositories containing 100,000 units of calcium penicillin in a cocoa-butter base used daily at bedtime for 7 to 10 days proved ample in the average case in this study. Prompt symptomatic improvement was achieved and maintained in most cases.

With the use of the suppositories a high content of glycogen was found in the cells of the vaginal fluid, and an unusually high percentage of the cells present was cornified. Both of these features may reflect an increase in the efficiency of the physiologic forces which normally operate in the vaginal tract to resist bacterial invasion. The role of glycogen in maintaining (through breakdown to lactic acid) an acid environment inimical to the growth of bacterial pathogens is well known. It is probable that the high percentage of cornified cells in the smear reflects an increased degree of surface epithelial cornification. This may serve to increase the capacity of the epithelium itself to resist bacterial invasion. Thus it appears that with the operation of the

antibacterial effect of penicillin the physiologic mechanisms which normally counteract focal infections in the vaginal tract are reinforced. In combating vaginitis and cervicitis there is apparently a synergistic relationship established between the antibiotic and the normal physiologic defenses of the vaginal tract. This may explain the efficiency of relatively small amounts of topical penicillin in treating these conditions.

It would appear that the disorder in the metabolism of glycogen which is reflected by vaginal smear glycopenia in the presence of focal vaginal infection is corrected by the action of an antibacterial agent. The inference is that the presence of the abnormal vaginal flora is the immediate cause of the glycopenia. Whether this condition results from an interference with estrogen action in promoting glycogen accumulation, as suggested by Mack, is problematical. There is also the possibility that glycopenia in the vaginal smear may result from a rapid rate of glycogen breakdown peripherally, glycogen accumulation continuing at a constant rate. This might result from the production of a high concentration of glycolytic enzymes by the bacteria present. The mechanism involved can only be hypothesized but it is apparent that an increase in the glycogen content of the vaginal tract accompanies the reduction of the bacterial flora.

The changes in vaginal cornification which occur during the normal menstrual cycle do not follow the usual pattern when penicillin suppositories are used. As Papanicolaou has shown, usually the C.I. is maximal in the late follicular period and low during the luteal phase of the cycle. However, when the suppositories are used in either the follicular or the luteal phase of the cycle a pronounced increase in the C.I. follows. The number and character of the cornified cells found in the smear are similar to those found in hyperestrinism.⁹ It is difficult to understand the mechanism effecting this change in cornification. That it would follow from a modification of the bacterial flora alone does not seem probable. Further investigation is being undertaken in an effort to clarify this effect of topical penicillin. It is notable that an extrinsic agent such as penicillin can alter the cells in the vaginal fluid in a manner identical to that usually attributed solely to estrogen activity. A high C.I.⁹ and high G.I.³ are both regarded as an indication of high estrogen activity. It is apparent that when isolated vaginal-smear findings are to be applied to estimations of relative degrees of estrogen activity the extrinsic factors which influence the cells seen in the smear must be borne in mind.

Detailed bacteriologic investigation was not undertaken in this study. Examination of stained smears prior to penicillin therapy showed a mixed bacterial flora consisting of bacillary rods, chains and clusters of cocci. Trichomonads were frequently observed. This was an apparently abnormal bacterial flora. However, since the normal flora of the vaginal tract is variable, a bacteriological standard of the desired end point in topical antibacterial therapy may be difficult to define. The results with the study of vaginal glycogen and the character of the vaginal smear suggest that the cytologic method provides an accurate and perhaps more physiologic criterion. When the antibacterial agent is employed there are variations in the concentration of glycogen present in the smear at different phases of the normal cycle but at almost any point throughout a G.I. of 50 or more is attained. Therefore, when the dose of penicillin employed results in a G.I. of 50 or more, it may be considered adequate for the restoration of physiologic conditions. This standard may also be readily applied by the physician if it is desired to follow the results of topical therapy objectively. Although the method was not used in the present study, Mack's iodine vapor technique³ is a simple and reliable office procedure for evaluating vaginal-smear glycogen.

Reactions to topical penicillin applied in the form of vaginal suppositories have been commented upon in various reports. The frequency of these reactions is not apparently as great, however, as in general dermatologic practice. Reactions to topical penicillin applied to the skin surface are encountered, according to Pillsbury,¹⁰ in 15 per cent of cases. Gottschalk and Weiss¹¹ found the initial patch test positive in 24 of 200 subjects. In contrast, Pierce¹² reports the use routinely of a single vaginal suppository containing 200,000 units of penicillin in 778 postpartum subjects without any local or systemic reactions. Abel and his associates¹ report 2 cases of urticaria in 19 nurses who used the suppositories, and 2 subjects in another series who developed vaginal itch, following initial improvement, during the treatment of vaginitis. Walter and co-workers² report the use of the suppositories by over 100 patients without serious reactions. In the present study 2 reactions were encountered in 15 subjects treated. Each reaction was mild in character. Symptoms promptly disappeared when the use of the suppositories was discontinued. It is noted that there were no reactions until after the suppositories had been used for periods exceeding ten days. It might be suggested therefore that for periods up to ten days vaginal suppositories containing penicillin may be used with relative safety.

Summary

Fifteen cases of chronic cervicitis with leucorrhea were treated with relatively small amounts of topical penicillin. Suppositories containing 100,000 units of calcium penicillin in a cocoa-butter base were used daily at bedtime for from 7 to 10 days. Symptomatic improvement was achieved and maintained in most cases.

The effects of topical penicillin upon the vaginal tract were evaluated by a combined morphologic and cytochemical vaginal smear study. Three effects were observed in the smear:

- A. Visible bacteria and leucocytes, initially prominent, disappeared.
- B. The epithelial cells present during and following therapy contained a high concentration of glycogen. In contrast, the vaginal smears were uniformly glycopenic prior to therapy.
- C. An unusual number of the epithelial cells present, during therapy in either the follicular or the luteal phases of the normal menstrual cycle, were cornified. Thus, the pattern according to which changes in epithelial cornification usually occur during the normal menstrual cycle was altered.

These results suggest that in combating focal vaginal infections, penicillin acts as an antibacterial agent and in the process reinforces the physiologic mechanism (vaginal glycogen) for the continued control of the vaginal flora. In some manner epithelial cornification is stimulated at the same time, apparently increasing the resistance of the epithelium to bacterial invasion. Thus a synergistic relationship is established between the antibiotic and the physiologic defense mechanisms of the vaginal tract. It is suggested that vaginal-smear glycogen study, which may be done as an office or clinic procedure,³ may provide an objective guide to this type of therapy.

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THE EFFECT OF PENICILLIN VAGINAL SUPPOSITORIES ON MORBIDITY IN VAGINAL HYSTERECTOMY AND ON THE VAGINAL FLORA*†

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THE vaginal approach for extirpation of the uterus and its appendages has been thoroughly discussed within recent years in the literature as well as before this Society. The reported low mortality rates make the operation a relatively safe procedure in the hands of those well trained in vaginal surgery. The postoperative morbidity, however, is still quite high, even in the hands of gynecologists of considerable experience.

Taking the usual standard of morbidity, namely, a temperature of or over 100.4° F. on any two days excluding the first twenty-four hours after operation, Campbell¹ in 2,798 vaginal hysterectomies indicated a mortality of 0.4 per cent and a morbidity of 36.5 per cent. Allen² in 640 cases had a mortality of 0.16 per cent and a morbidity of 26.4 per cent. Others^{3, 4, 5} reported morbidities varying from 28 to 42 per cent.

Since in most cases no adequate explanation could be found for the febrile morbidity and since the mortality has been very low, numerous gynecologists are of the opinion that the conventional method of reporting morbidity rates should not apply to vaginal operations.^{1, 2} Nevertheless, a sudden rise in temperature which may last for several days causes an undue amount of anxiety. It can also be at least suspected that the febrile course is most likely the result of toxicity produced by so-called "normal" bacterial habitants in the vagina which could not be eliminated by the usual preoperative preparation.

Because penicillin vaginal suppositories have been recommended in the treatment of acute vaginitis^{6, 7} and in the reduction of puerperal morbidity due to genital-tract infection,⁸ it was felt that their addition as a local adjunct in preparing the vaginal tract for surgery might be of aid in reducing the postoperative morbidity in vaginal hysterectomies.

Material and Results

On the gynecologic service at the Mount Sinai Hospital, the usual preparation for vaginal surgery included evaluation of the general physical condition of the patient, a soapsuds enema, and a 1 per cent iodine douche the night before operation. A careful cleansing of the vagina and cervix with tincture of green soap, followed by painting with tincture of mercuric chloride was done

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immediately before the operative procedure was started. Blood transfusions were used liberally whenever indicated and local foci of infection were attended to whenever possible.

With this type of management, a personal series of 56 vaginal hysterectomies resulted in no mortality but a morbidity of 37.5 per cent. The 21 cases of morbidity ran an average of 5.8 days. In 8 patients urinary-tract infection was found and in 13 patients no apparent cause could be determined. None of these patients had any detectable injury to the ureters, bladder, rectum, or bowel. They all had to be treated with sulfonamides or antibiotics. The average hospital stay was 11.8 days.

Beginning in September, 1947, a cocoa-butter suppository containing 100,000 units of crystalline potassium penicillin G was added to the usual vaginal preparation as outlined above. The suppository was inserted deep into the vagina the night before operation as soon as the enema and iodine douche were expelled and absolute bed rest was instituted. This procedure was followed in 67 consecutive cases. In the subsequent 33 cases the iodine douche was eliminated. So far, this series consists of 100 nonselected consecutive cases. The effects on morbidity were encouraging enough to consider them worth while reporting. The operative procedures are summarized in Table I. Of the 65 personal cases, 61 had spinal anesthesia and 4 had general anesthesia. Thirty-five patients were operated upon by Drs. A. E. Kanter and A. H. Klawans in order to accelerate this study during the last few months. Most of the patients in the latter group received general anesthesia. The operative technique of Dr. Kanter, which is similar to that of Dr. N. Sproat Heaney, was closely followed by the essayist in most of the operative procedures.

TABLE I. SUMMARY OF OPERATIVE PROCEDURES

1. Simple vaginal hysterectomies	10
2. Vaginal hysterectomy, anterior colporrhaphy, perineorrhaphy	30
3. Vaginal hysterectomy, anterior colporrhaphy	8
4. Vaginal hysterectomy, perineorrhaphy	14
5. Vaginal hysterectomy, anterior colporrhaphy, perineorrhaphy with removal of one or both adnexa	6
6. Vaginal hysterectomy, anterior colporrhaphy, removal of one or both adnexa	7
7. Vaginal hysterectomy, anterior colporrhaphy, hemorrhoidectomy	1
8. Vaginal hysterectomy, perineorrhaphy, biopsy of breast	1
9. Vaginal hysterectomy by morcellation	5
10. Vaginal hysterectomy by morcellation, anterior colporrhaphy, perineorrhaphy	4
11. Vaginal hysterectomy by morcellation, anterior colporrhaphy	3
12. Vaginal hysterectomy by morcellation, anterior colporrhaphy removal of both adnexa	1
13. Vaginal hysterectomy, removal of one or both adnexa	8
14. Vaginal hysterectomy, hemorrhoidectomy	1
15. Vaginal hysterectomy, bilateral bartholinectomy	1
Total	100

The age of the patients varied from 31 to 74 years, the average age being 47.8. There were 91 multiparas and 9 nulliparas. The lesions consisted of 14 cases of complete procidentia, 4 cases of descensus uteri, 59 fibromyomas of the uterus, 54 cervicitis with or without erosion and/or Nabothian cysts, 10 fibrosis uteri, 42 cystoceles, 27 rectoceles, 12 adenomyosis uteri, 7 cervical and 8 endometrial polyps, 1 dermoid cyst of an ovary, 1 case of endometriosis of both Fallopian tubes and ovaries, 1 bilateral chronic bartholinitis, and 1 benign breast tumor.

There were no deaths. The postoperative hospital stay ranged from seven to fifteen days, the average being 9.8 days. Twenty-one remained in the hos-

pital beyond ten days. A few could have been discharged earlier but remained in the hospital to suit their convenience. Twelve patients had some difficulty with residual urine after removal of the indwelling catheter and one was treated for phlebothrombosis of the right lower extremity.

Seven patients had a febrile morbidity, three of which cases were caused by a cystitis that responded well to urinary antiseptics or sulfonamides. In three other patients the cause of the elevation could not be determined. Two of these required no additional therapy. The third responded well to penicillin and sulfonamides. The seventh patient had a urinary infection with a phlebothrombosis of the right lower extremity and recovered after receiving penicillin and anticoagulants for seven days. One patient of the series had an uneventful postoperative course but developed a generalized peritonitis caused by a perforated abscess involving the sigmoid and the left Fallopian tube and ovary sixty-three days after operation. The abscess and peritoneal cavity were drained and with the aid of antibiotics and sulfonamides the patient recovered. It was thought that the complication resulted from a diverticulitis of the sigmoid or from an acute exacerbation of a chronic salpingo-oophoritis. This case was excluded from the morbidities.

TABLE II. EFFECT OF A 100,000-UNIT PENICILLIN SUPPOSITORY OF THE FLORA IN 83 VAGINAL CULTURES

TYPE OF ORGANISM	NO. OF TIMES FOUND BEFORE SUPPOSITORY	NO. OF TIMES FOUND 12 TO 14 HOURS AFTER SUPPOSITORY
<i>Staph. albus</i>	24	2
<i>Staph. aureus</i> , nonhemolytic	19	4
<i>Staph. aureus</i> , hemolytic	33	2
<i>Staph. anaerobic</i>	0	1
<i>Alpha viridans</i> streptococci	22	1
Beta-hemolytic streptococci	12	2
Streptococci, nonhemolytic, anaerobic	3	1
Other cocci	13	2
<i>E. coli</i>	19	8
<i>Proteus vulgaris</i>	2	0
<i>Aerobacter aerogenes</i>	9	6
<i>Pseudomonas</i>	7	5
<i>Paracolonbacterium coliforme</i>	2	0
Unidentified gram-negative rods	3	2
<i>Bacteroides</i> species	2	0
Diphtheroids	20	7
Lactobacilli	18	4
<i>B. subtilis</i>	5	2
<i>Candida albicans</i>	7	7
Other yeasts	8	8

The encouraging early clinical results prompted the investigation of the effect of penicillin suppositories on the vaginal flora. Vaginal and cervical cultures were made in brain heart infusion broth, in Brewer's thioglycollate, in Sabouraud's dextrose agar, and phytone-dextrose-serum agar for Lactobacilli⁹ and organisms identified by the usual aerobic and anaerobic procedures. These were taken before the patient received any vaginal treatment, and repeated just before operation, approximately twelve to fourteen hours after a penicillin suppository was inserted vaginally. In the first 50 cases a 1 per cent iodine douche was employed before the suppository was inserted. As the efficacy of the penicillin became apparent, the iodine douche was eliminated in the subsequent 33 cases. The bacteriologic end results were approximately the same. Of the 83 cases studied, 40 showed no growth after the penicillin, whereas all of the cultures contained some organisms before the suppository was used. The detailed culture results are shown in Table II. Pyogenic cocci were almost completely

inhibited. The enterobacteriaceae were found forty times in the first cultures and nineteen times after the penicillin. It is realized that some of these intestinal organisms may represent vulvar contamination. Lactobacilli were much less frequently found in the postpenicillin cultures. This may be due to pH variation in the vaginal tract rather than to any bactericidal effect. The yeasts, as expected, were not affected by the addition of penicillin.

While this study was going on, a comparable series of 210 vaginal hysterectomies were performed by others at this hospital. Except for the preoperative use of the penicillin suppository, these patients received approximately the same routine presurgical management. They, however, had an average of 11.2 post-operative hospital days and a morbidity of 34.8 per cent with an average of 4.3 febrile days per morbid patient. Of the 73 febrile cases, 53 had to be treated with parenteral antibiotics and/or sulfonamides. There were no mortalities.

Comment

It is realized that a series of 100 cases is still too small to permit decisive conclusions. Nevertheless, the fact that there were only 7 with a temperature rise up to 101.2° F., which lasted from two to four days after operation, and the fact that there were only 4 patients who required subsequent administration of antibiotics or sulfonamides seem to indicate that the penicillin suppository was responsible in reducing the author's morbidity from 37.5 per cent to 7 per cent. This rate also compares favorably with the 26 to 42 per cent morbidity reported in the literature and with 34.8 per cent in the control series. There was no untoward reaction from the suppositories in any of the cases. The method is simple, inexpensive, and is worthy of a trial in all types of vaginal operations.

The results in the bacteriologic studies speak for themselves. The almost complete inhibition of the pyogenic cocci in the cultures obtained a few hours after a penicillin suppository was inserted adds further reasonable belief that the suppository is a valuable adjunct in clearing the vaginal tract of many bacteria that may cause morbidity following vaginal operation.

Summary and Conclusions

1. A cocoa-butter suppository containing 100,000 units of crystalline potassium penicillin G was inserted vaginally from twelve to fourteen hours prior to operation in one hundred consecutive, nonselected vaginal hysterectomies.
2. According to the usual standard of morbidity as outlined by the American College of Surgeons, this series had a 7 per cent morbidity in contrast to the reported morbidities which vary from 26 to 42 per cent.
3. With employment of the same preoperative preparation prior to the use of the penicillin suppository, the morbidity in fifty-six personal vaginal hysterectomies was 37.5 per cent and in a control series of two hundred ten cases the morbidity rate was 34.8 per cent.
4. The bacteriologic and clinical studies support the belief that penicillin vaginal suppositories are of value in reducing morbidity when employed as an adjunct in preoperative preparation in vaginal hysterectomy.

I wish to extend thanks to Drs. A. E. Kanter and A. H. Klawans for their generosity in assigning cases for this study, to Dr. I. Davidsohn, for making the laboratory facilities available, to all the members of the gynecologic staff for allowing the review of their cases as a comparative study, and to Mr. M. Goldin, Bacteriologist, for carrying out the bacteriologic aspects of the study.

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30 NORTH MICHIGAN AVENUE

Discussion

DR. GEORGE H. GARDNER.—We are agreed that vaginal hysterectomy is a relatively innocuous surgical procedure and is attended by a negligible mortality even though, according to present standards, there is a considerable morbidity which is usually reported to be between 30 and 40 per cent. Do you realize that we have just been told that a slight variation in the usual preoperative preparation of patients leads to an 80 per cent reduction in postoperative morbidity? Only 7 per cent were morbid in the series in which penicillin vaginal suppositories were used preoperatively, in contrast with a 35 per cent morbidity in another group operated upon during the same period of time, at the same hospital, but by a different group of gynecologists who did not use preoperative penicillin. There is much less morbidity among patients subjected to a simple vaginal hysterectomy, than among those who have extensive vaginal plastic procedures in addition to the hysterectomy; but I must remind you that only 10 per cent of Dr. Turner's group had a vaginal hysterectomy alone and that 75 per cent had additional plastic procedures. At Wesley we have not used preoperative penicillin suppositories long enough to have an opinion regarding their efficacy, but we have noted a marked reduction in morbidity in recent years when, incidentally, we have given intramuscular penicillin routinely for a few days after extensive vaginal plastic operations; this obviously is much more uncomfortable and much more expensive than suppositories. Furthermore, I am impressed by the total absence, in Dr. Turner's series, of postoperative drainage from an abscess in the operative site. I have always regarded this complication as the result of infection in a hematoma.

Dr. Turner's conclusions would be much more convincing if he and his group had used penicillin suppositories only in every other case, and had then reported on the morbidity in these two, otherwise comparable, series of patients. Finally, in my humble opinion, operative technique, and not manner of using antibiotics, still remains the all-important factor in determining mortality, morbidity, and end results from any operative procedure.

DR. EDWARD ALLEN.—We have been extremely interested in this particular phase of this subject for many years. We have repeatedly stated that our feeling was that, if we could operate only upon those patients whose vaginal flora was normal, in whom distant foci of infection had been eradicated and hemostasis was correct, our morbidity based on proper criteria would be practically nil following vaginal hysterectomy. We still believe it is essential to delay a vaginal operation until the vaginal flora is as normal as we can get it, in the same way as we would delay an elective abdominal operation until a furunculosis of the abdominal wall was well again.

Several years ago we began a study in which we were trying to sterilize the vagina with various chemicals such as Zephiran. Solutions of this type seem only to reach the surface bacteria because cultures taken at the onset of operation by swabbing the vaginal mucous membrane were almost regularly sterile or grew only a few colonies. Those taken halfway through or on completion of the operation revealed almost as many colonies as before the

patient was scrubbed and the solutions applied. I wonder if Dr. Turner took his cultures at the beginning or the end of operation.

It would seem wise in any method of routine medication to take into account those few patients who developed sensitizations or reactions to the agent employed. I should like to ask Dr. Turner if he can tell us what are the probabilities of this happening by the insertion of large doses of penicillin into the vagina. Sensitization which precludes use of the drug in subsequent emergencies has been reported frequently following oral treatment.

The following tabulation shows the results in my own cases operated upon during the same period of time for comparison with the essayist's results and also the morbidity rate of the larger personal group which I reported before this Society last year.

TABLE I

NO. CASES	MORBIDITY
640 Previously reported	26.4%
51 Before using suppositories	17.0%
54 Using suppositories	8.0%

The decline in morbidity may not even be suggestive on account of the small number of cases in the last two groups but it would seem to indicate that while improvement in technique has accounted for about 9 per cent in morbidity, the use of penicillin has further decreased the febrile reactions 18 per cent over those in cases operated upon before during 1948.

I have divided the morbidity in these two groups of cases according to the procedures carried out in the individual case in the same way as I did in the large group. I believe the results indicate again that the accessory surgery is a very important equation in the postoperative febrile reaction.

TABLE II. FIFTY-ONE CASES WITHOUT PENICILLIN

CASES	NO. DAYS	MORB.
1. Vaginal hysterectomy (only)	2	1
	1	2
	1	3
	3	1
	1	2
2. Vaginal hysterectomy with adnexal operation	2	2
Total	10	11

TABLE III. FIFTY-FOUR CASES WITH PENICILLIN

	CASES	DAYS
1. Vaginal hysterectomy (only)	1	2
2. Vaginal hysterectomy with morcellation	2	1 each
3. Vaginal hysterectomy with perineal repair (Rectal prolapse operation)	1	4
Total	4	8

The standard of morbidity used in this and other reports indicates only febrile reactions. Many of them were transitory bladder infections. I believe the term *morbid* should be reserved for those conditions which require longer than usual hospitalization or leave the patients with disagreeable sequelae. Only two of these 105 cases by these criteria were morbid.

DR. AARON E. KANTER.—I was very skeptical when the essayist approached me and told me of his results in reducing postoperative morbidity by the preoperative use of penicillin locally. However, I encouraged him to proceed with his study. When he brought his results to me, I was astounded. The figures were difficult to believe. I brought the

work to the attention of the staff at the Presbyterian Hospital and it was decided that we give this procedure a trial. I am reporting on 100 consecutive cases operated upon by all the members of the gynecologic staff of the Presbyterian Hospital. In this group there were 23 vaginal hysterectomies without added surgery while in the other 77 cases there were a variety of added operations including anterior plasties, posterior plasties, defundectomies, bilateral or unilateral salpingectomy or oophorectomy, and resection of endometriosis. In a group of cases of that diversity, there was certainly plenty of opportunity for the development of morbidity, yet only 12 per cent of the patients showed any postoperative temperature rises. It is interesting to note here that of the 12 patients with morbidity, 5, or 42.5 per cent, had endometriosis along with their other pathology and along with the various complications that endometriosis can produce. The average length of morbidity was two and one-fourth days, with only 3 patients showing temperature rises for three days. Previously, it was not uncommon for patients to run fevers for seven to ten days. Not only was the total number of patients showing morbidity low but the height of the temperature curves was also low. I do not feel that improvement in surgical technique alone could have been responsible for this significant reduction in morbidity. The probable reason for the good results was the reduction in the number of pathogenic bacteria.

One thing I do not like about morbidity statistics associated with gynecologic patients is the standard used. A patient may have a temperature up to 100.4° or even 101° F., and still be and feel perfectly well. In considering postoperative reactions we must think of other factors such as early ambulation, early feeding, lack of gas pains, and early completion of total and partial disability provided by doing the surgery through the vagina. This added safety is just another incentive to those of us who do all possible pelvic surgery by the vaginal route.

DR. H. CLOSE HESSELTINE.—The discussion has been covered quite adequately except for one or two points. The tabulation indicates that 500,000 units of penicillin inserted vaginally will produce therapeutic blood levels but do not give a sustained level. If one were to maintain these levels of penicillin by the vaginal route, it would require 20 suppositories each of 500,000 units (3 to 4 every 4 hours per 24 hours) to maintain a therapeutic level. This is expensive and the level is unpredictable and thus unsatisfactory.

The point of judging the bactericidal effect must be guarded. There is certain difficulty in taking cultures when any medicament is inserted in the vagina. There may be sufficient medicament to prevent bacterial growth in the culture. There may be so much cocoa butter in the culture material that one does not get a true bacterial sample. The suppositories will dilute the contents of the vagina and thus give the impression of bactericidal value. Moreover, some organisms found in the vagina, as the *E. coli* and *B. aerogenes* may grow in penicillin solution. These points should be considered.

Another point is the use of the word yeast infection. I once used the word *yeastlike*. Yeasts are definitely nonpathogenic and cause no trouble in the vagina or in or under the skin. Yeasts are as different from the *Candida albicans* or *Monilia* as are bacilli from cocci.

DR. EDWIN J. DE COSTA.—We have been equally skeptical about the prophylactic value of penicillin suppositories. However, with the cooperation of the Gynecologic Department of Michael Reese Hospital, we administered penicillin suppositories to a small controlled series of patients. Alternate patients received one suppository the night before surgery. This series included more than vaginal hysterectomy; it included 35 total abdominal hysterectomies. We will consider this group only. Any patient who developed a temperature of 100.4° F. or over was classed as morbid. Ten out of 16 patients who received vaginal suppositories did not have a temperature of 100.4° at any time. In the control series, 15 out of 19 had a temperature of 100.4° or higher. This series is small but indicates, however, that a single vaginal suppository containing 100,000 units of penicillin given the night before surgery will appreciably reduce postoperative morbidity.

DR. TURNER (Closing).—Dr. Allen asked whether the penicillin suppository may sensitize the patient against penicillin. I am not able to answer at the present time. As far as it is known, none of our patients developed any reactions to date.

THE RESULTS OF TREATMENT WITH Rh HAPTEN

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AFTER the encouraging report by Loughrey and Carter¹ on the use of a substance assumed to be Rh hapten for treating an edematous erythroblastotic baby, it was decided to use the substance in the treatment of Rh-sensitized pregnant women.

Because of the scarcity of the preparation we elected to treat only those severely sensitized women who had lost one or more babies to the disease. Although one finds an occasional report of an Rh-positive baby surviving after the death of several of its predecessors,^{2, 3, 4} it is generally observed⁵ that subsequent babies of the same genotype tend to be equally if not more seriously involved. It was, therefore, believed that, if even a small series of such patients could be treated with uniform success, the worth of hapten might be established. As the study progressed it became obvious that the better time to begin treatment was early in pregnancy, before the development of any Rh specificity in the fetal erythrocytes. Diamond places this in the third month of gestation.⁶ And, since we had a number of sensitized patients in the interim between pregnancies, we felt the best method would be to reduce the antibody titer to zero, allow them to become pregnant, and administer hapten throughout pregnancy to keep the titer at zero. The results will be described in the case histories that follow.

Materials and Methods

The hapten was made after the method of Carter,^{7, 8, 9} with subsequent addition of two steps employed by Goldsmith.^{10, 11} The first step was ultraviolet irradiation overnight of the lipid residue from the ether evaporation process. The second was the extraction with warm 95 per cent ethanol of the soluble portion of this residue. After evaporation of the alcohol, the residue was weighed and placed in ampules made up to contain 200 mg. of hapten in 1 c.c. of 95 per cent ethanol.* For administration this solution was drawn into a syringe containing 20 c.c. of sterile normal saline, mixed, and given slowly into the gluteus maximus muscle.

A commercial laboratory preparation was put up in two ways. One was 100 mg. of purified hapten in 1 c.c. of sesame oil. This was nonirritating when given intramuscularly, and we saw no reactions from the oil. The other was 100 mg. of purified hapten in 95 per cent ethyl alcohol. It was given in the same way as our preparation except that 1 c.c. of 1 per cent procaine was added.

The Kolmer complement-fixation test was used to assay our preparation for potency, as suggested by Carter.⁹ We were unsuccessful in applying this technique even though each detail was carefully followed and adequate con-

*Lots used after Aug. 1, 1949, were made by this method.

trols were run. In only nine out of fifty lots could we demonstrate any fixation of complement. In one instance two lots, which we considered negative, were sent to Carter, who reported potency in dilutions of 1:1,000. On another occasion a sample, which we were forced to call negative, was sent to Goldsmith for assay. The report from his laboratory showed activity in dilutions of 1:4,000.

The principal method for determination of Rh antibody titers was the conglutination test.¹² The cells used were fresh, type O Rh positive, pooled from three or four bloodbank donors. Only cells less than three days old were used. In the beginning of our study the diluent used for the patient's serum and for the Rh-positive cell suspension was 20 per cent bovine albumin in normal saline. Due to the extreme viscosity of this medium, AB male plasma was used instead. Then the combination of AB plasma for the patient's serum dilutions and 20 per cent bovine albumin for the cell suspension was adopted.¹³ This medium is referred to as "plasma-albumin," and seems to provide the most consistent and desirable source of conglutinin.

In a few instances, samples of blood were examined for saline agglutinins, as well as for the individual conglutination titer of antibodies against C, D, and E.

CASE 1.—Mrs. C. G., aged 38 years, para iv, gravida vi, was found to be type O, cde/cde. The husband was type O, probable genotype CDe/CDe. The Kahn test was negative on both. The patient delivered normal term children in 1933 and 1935 who are living and well, genotype CDe/cde. In 1938 she had lobar pneumonia, and was given two transfusions of her husband's blood and one from her husband's brother. In 1939 she delivered a 6-pound male at term that died the third day of erythroblastosis. In 1941 a 7-pound term female was delivered that survived after multiple small transfusions of the father's blood. The child is normal, type O, genotype CDe/cde. In 1945, labor was induced at eight months and the child died on the second day of erythroblastosis. The baby was transfused with type O, Rh-negative blood. In 1946 the patient miscarried at 3½ months.

We first saw this patient on Nov. 8, 1948, when the titer was 1:64. She had a conglutination titer elsewhere of 1:16 on Sept. 25, 1948. Our own hapten was given in doses averaging 225 mg. at weekly intervals starting Nov. 10, 1948, and continuing through Dec. 14, 1948, when this dose was given twice weekly until Jan. 22, 1949, when a final dose of 502 mg. was given. During the entire period twice weekly bovine albumin conglutination titers averaged 1:16, and never went below 1:8.

She delivered at term January 23 at 12:04 A.M. The child breathed and cried spontaneously, appeared normal except for slight pallor, and weighed 5 pounds, 10 ounces. Conglutination titer on the cord blood was 1:2. The blood type was O, CDe/cde. Hapten, 200 mg. in 50 c.c. normal saline, was given in the back muscles at 12:30 A.M. and repeated at 9:00 A.M. and 9:00 P.M. One hour after birth the peripheral blood showed 4.53 million red blood cells with 14.5 Gm. of hemoglobin and 37 nucleated red blood cells per 100 white blood cells. The baby was not transfused until 4:00 P.M. that day when the count showed 3 million red blood cells and 9 Gm. hemoglobin. Then 50 c.c. of whole citrated blood were given from the baby's father, which elevated the count to 5.13 million red blood cells. There was a gradual decline until the morning of January 26, when the erythrocyte count again reached 3 million. The above type of transfusion was repeated. Earlier that morning the baby had begun to have attacks of cyanosis. X-ray examination of the chest showed lobular infiltration throughout the entire right-lung field and upper half of the left-lung field. The attacks of cyanosis became more severe in spite of oxygen therapy until the baby died at 5:50 A.M., Jan. 27, 1948, with bloody discharges from the nose and mouth. Autopsy revealed "hemorrhagic pneumonic consolidation bilaterally; erythropoiesis of liver, spleen, and thymus; small renal infarction; and bile stasis in the liver. Diagnosis: erythroblastosis

fetalis." Ideally haptén should have been started earlier during pregnancy and given longer to the baby. At least there was no apparent benefit from it as used in this case.*

CASE 2.—Mrs. D. O., aged 23 years para ii, gravida iii, type A, cde/cde, husband type O, probable genotype CDe/cDE, delivered a normal male infant May 6, 1946. This child is type O CDe/cde. Her second baby was a term male born Sept. 28, 1947, that lived 9 hours. The diagnosis of erythroblastosis was made at autopsy. The type of the baby was not determined.

In the last pregnancy the estimated date of confinement was April 24, 1949. We first saw the patient on Dec. 31, 1948, when the conglutination titer was 1:16. Beginning Jan. 28, 1949, she was given our haptén, 300 mg. weekly, until April 6, 1949, when 800 mg. were administered. Weekly bovine albumin titers were usually 1:8, varying from 1:2 to 1:16. No downward trend was observed although at delivery the titer was 1:2.

On April 6, 1949, following a medical induction, she delivered spontaneously a living female infant weighing 7 pounds, 6 ounces, which breathed and cried spontaneously. Cord-blood studies revealed the baby to be type A, cDE/cde. Coombs test on the cells was positive; conglutination titer 1:4; icterus index 8 units. The peripheral blood one hour after birth showed 3.25 million red blood cells, 77 per cent hemoglobin, 25,800 white blood cells, and 42 nucleated red blood cells per 100 white blood cells, at which time 200 mg. of haptén in 50 c.c. of normal saline were given in the back muscles. This was followed in 2½ hours by 65 c.c. of citrated type O cde/cde blood from a female donor. The icterus index at the start of the transfusion was 40 units, rising to 65 units two days later. Fifty c.c. transfusions from the same donor were given on April 13 and April 26, and on the latter date 200 mg. of our haptén were given in the aforementioned manner. The erythrocyte count was well maintained until the day before the last transfusion when it had dropped to 3.5 million.

The child had a stormy course, almost dying the morning of April 10, but improved following a spinal tap. When discharged May 5, 1949, the baby was in apparent good general condition but with breathholding on crying. One year later the child was definitely retarded and was flaccid.

It is possible that the genotype of the first two children was CDe/cde, accounting for the short life of the second baby. The last child was perhaps able to survive because its genotype was cDE/cde, there being antibodies only to C and D. There is no evidence in this case that haptén was effective. It is a matter of conjecture what earlier administration would have accomplished.

CASE 3.—Mrs. B. S., aged 27 years, type A cde/cde, para iii, gravida iv, husband type O, probable genotype CDe/cDE, had normal term pregnancies in 1941 and 1943. In January of 1947 she had a missed abortion and, for reasons unknown to us, was transfused. A reaction followed and the patient delivered a macerated fetus the next morning, eight months after the last menstrual period. After delivery she was again transfused and had a mild reaction. The transfused blood was probably Rh positive but there is no record.

In this pregnancy she was due May 29, 1949. Her conglutination titer was reported 1:4 from another laboratory in November, 1948. Starting Feb. 3, 1949, she was given 300 mg. of our haptén every two weeks for four doses, the last being given March 26, 1949. The titer with bovine albumin varied from 1:16 to 1:64 with no evidence of a downward trend. When it became evident the fetus had died, treatment was discontinued. She finally delivered a macerated fetus (C.R. length 16 cm.) on June 17, 1949. The pathologic report was not illuminating because of tissue autolysis. During the short time she was treated we produced no significant change in her titer.

CASE 4.—Mrs. A. F., aged 40 years, was para v, gravida vi, type A, cde/cde. The husband was type O, probable genotype CDe/cde. In 1941 she delivered a normal living infant. In 1942 a term infant was born that died on the fifth day with a diagnosis of

*The pediatric management was in other hands. Except for the use of haptén, they were treated in much the same way as the mother's previous children, and in most instances by the same physician.

purpura. In 1945 she delivered a premature baby at seven months that died the same day. In 1946 she delivered a living female at term with moderately severe erythroblastosis that survived. In 1947 a living female infant was born at term that died of erythroblastosis the third day.

In this pregnancy she was not seen until Feb. 28, 1949, when the conglutination titer was 1:16. The estimated date of confinement was May 16, 1949. Our hapten was given in weekly 300-mg. doses starting March 5, ending with a dose of 400 mg. April 30. Bovine albumin titers taken at weekly intervals ranged from 1:2 to 1:16, with no saline agglutinins. The titer was 1:8 with the husband's cells April 27, 1949. Prior to this there had been a gradual downward trend. On May 3 labor was easily induced by Pitocin and delivery accomplished under saddle-block anesthesia. The child, a living female, born with spontaneous respiration and cry, was extremely pale, moderately edematous, weighed 7 pounds, 2 ounces, and had old petechiae and ecchymoses over the entire body. The cord blood was type O cDe/cde with an icterus index of 15 units. Shortly after birth the peripheral blood showed 1.72 million red blood cells, with 45 per cent hemoglobin, 60,200 white blood cells, and 272 nucleated red blood cells per 100 white blood cells. The baby was promptly transfused with 90 c.c. of type O cde/cde blood, and seven hours later 70 c.c. of a concentrated cell suspension were given from the same donor. Twenty-four hours after birth 50 c.c. of blood from the same donor were given along with 200 mg. of our hapten, the latter given as described before. When the baby was 2 days of age, the icterus index was 59 units. The infant's course was rapidly downhill, death coming 60 hours after birth, with frothy blood issuing from the mouth and nose in the same manner as in the case of her previous child. Autopsy showed generalized jaundice and kernicterus; hemorrhagic infiltration of both lungs with atelectasis and compensatory vesicular emphysema; hemorrhagic infiltration of the papillary muscle of the right cardiac ventricle; congestion of the liver, congested hyperplastic spleen, multiple ecchymoses of serous and mucous membranes. There was such a gratifying drop in the titer that we thought the baby might be Rh negative. Even if hapten had been effective in eliminating all antibodies from the maternal blood, the treatment came too late to be of benefit. The drop in titer may have been due to hapten, but we believe this patient reacted similarly to the grade iii of Primrose, Van Drosser, and Philpott,¹⁴ in which group they hold out very little hope for the baby.

CASE 5.—Mrs. M. J., aged 28 years, was para iv, gravida vi, type O, cde/cde. The present husband is type O cDe/cde. There were two previous husbands whose types are unknown. The previous obstetrical history follows:

First husband	{	1938 Term pregnancy, baby normal, severe pre-eclampsia.
		1939 Term pregnancy, baby normal, albuminuria.
		1942 8½-month pregnancy, erythroblastosis, albuminuria. The infant died on the thirty-eighth day of pneumonia.
		1946 Miscarried at 6 weeks, no complications.
Second husband—1947 7-months, hydrops fetalis, severe pre-eclampsia.		

In the present pregnancy the estimated date of confinement was July 8, 1949. The patient was first seen Jan. 24, 1949, when the conglutination titer was 1:256. She was given our hapten preparation in 300 mg. doses twice weekly starting Jan. 31, and continuing to April 2, after which 200 mg. were given three times weekly until delivery. Weekly titers varied considerably but the general trend was from around 1:256 at the outset to 1:1,024 at delivery time. Her titers were checked by all three methods with comparable findings. No saline agglutinins were found. The titer with the husband's cells March 5, 1949, was 1:128 and was negative with cDe/cdE cells.

The baby is type O, cde/cde. Coombs test on the baby's cells at birth was negative, and the baby was normal in every respect. The typing was verified at 6, 8, and 32 weeks of age. It is interesting that in this pregnancy there was no albuminuria or elevation of blood pressure such as occurred with the previous advanced pregnancies.

This case is most interesting in that the titer rose to quite high levels. It could be attributed to antigenicity of the hapten preparation, but patients in Cases 1 to 4 were treated

with some of the same lots without such a response. At least one can say we did not succeed in bringing the titer down even when there was no specific Rh antigen in the baby. The rise more likely represents an anamnestic response to pregnancy per se,^{15, 16} as has previously been reported.^{17, 18}

CASE 6.—Mrs. G. H., aged 24 years, type B cde/cde, not pregnant, whose husband is type O cDE/cde, delivered her first child, which was normal, at term, May 20, 1946. The second term child born Nov. 19, 1947, died of erythroblastosis a few hours after birth. On Jan. 9, 1949, she delivered a macerated 31-week fetus. Our haptén was given, 200 mg. weekly, June 11, 1949 to Aug. 15, 1949, when purified haptén in oil was instituted. This was continued, 200 mg. weekly, until Dec. 16, 1949, when the same preparation in alcohol was given in like dosage through Jan. 31, 1950. Titers by the plasma-albumin method taken at weekly intervals stayed in the zone from 1:256 to 1:512. Saline agglutinins ranged from negative to 1:8. One could observe no lowering of titers after giving 6,800 mg. over a period of 7½ months.

CASE 7.—Mrs. F. S. is type A cde/cde. Her husband is probable genotype cDE/cde. In 1943 she had an ectopic pregnancy and was transfused twice. She became pregnant and delivered at term in 1947 a child which died of erythroblastosis the sixth day. In 1948 she miscarried at four months. During this study she was not pregnant. Haptén dosage and dates were almost identical to those in Case 6. Her titers, however, stayed in the range from 1:8 to 1:64, with saline agglutinins negative to 1:4. She, likewise, showed no negation of titer from haptén administration.

CASE 8.—Mrs. S. W., aged 33 years, para iii, gravida iii, not pregnant, type O cde/cde, husband, type O, probable genotype cDE/CDe, delivered a normal term baby in 1940; a full-term stillborn infant in 1941; and in March of 1949 a full-term stillborn infant with fetal hydrops. She was given 200 mg. purified haptén in alcohol three times weekly from Dec. 24, 1949, through March 4, 1950. The initial albumin-plasma titers were 1:128 and they gradually fell to 1:8 at the end of treatment. Of all the patients she represents the most satisfactory drop in titer although it did not become negative after administration of almost 4,000 mg. This was in the absence of any stimulation from pregnancy.

CASE 9.—Mrs. B. F., aged 34 years, type O cde/cde, husband type O, Rh positive, delivered a normal term baby in 1942. In 1945 she delivered a term stillborn erythroblastotic baby. In 1946 she delivered a term baby which was erythroblastotic but which survived. In 1947 a term baby died of erythroblastosis on the second neonatal day. She was not pregnant during this treatment which consisted of 200 mg. of purified haptén in alcohol at weekly intervals from Dec. 20, 1949, through Feb. 24, 1950. Plasma-albumin titers remained unaltered at 1:256 during this time. Haptén apparently had no effect in this case.

CASE 10.—Mrs. M. R., aged 25 years, para v, gravida vi, type O cde/cde, whose husband is type O CDe/CDe lost her last three babies from erythroblastosis. The last one had fetal hydrops. At delivery, May 6, 1949, her conglutination titer was 1:8. One month later it was 1:1,024. The estimated date of confinement for the present pregnancy is June 22, 1950. Our haptén was given intramuscularly in saline, 400 mg. every two hours for four doses, then 200 mg. every two hours for four doses, making a total of 2,400 mg. of haptén given in fourteen hours. The titers remained unchanged at 1:64 to 1:128 after this massive treatment.*

CASE 11.—Mrs. I. W., aged 38 years, type O cde/cde, whose husband is type A, probable genotype CDe/CDe, delivered a living child in 1946. In the last pregnancy she was due Nov. 15, 1949. On Sept. 24, 1949, her titer was found by another laboratory to be 1:8 which was promptly checked and verified in our laboratory. Haptén was recommended but the husband did not want it used. Six subsequent plasma-albumin titers were negative, and a normal child was born Dec. 4, 1949, with no clinical evidence of erythroblastosis

*Since this paper was submitted, the patient delivered a macerated fetus, April 20, 1950. Life was last felt about the time of the haptén administration two months before delivery.

or anemia. Its type is A, CDe/cde, and the Coombs test on the cells of the cord blood was negative. Had hapten been used, one might have given it credit for producing a negative titer and preventing all evidence of erythroblastosis in the baby.

Comment

The study of these cases has brought out several points, all previously reported, but which are unknown or not believed by many who are called upon to conduct a sensitized Rh-negative woman through pregnancy.

Case 5 illustrates that a rising titer during pregnancy is not conclusive evidence that the fetus is Rh positive. Along with other reported instances by Kendig,¹⁷ and Mollison,¹⁸ it should serve to stay the hand of those prone to do abortions in such instances.

In another case to be reported elsewhere by Dippel, there was a rise in the maternal conglutination titer against D, although the fetus later was observed to be of genotype Cde/cde. Once a woman has been previously sensitized, to C and D for example, a study of the specific antibody titers will give no positive indication of the genotype of the fetus. The antibodies may rise independently of the specific antigen or antigens in that pregnancy.

Both the pregnant and nonpregnant sensitized women may show considerable variation in titers if followed closely. If the titer is 1:8 from the onset of pregnancy, and if the fetal erythrocytes contain antigens specific for these antibodies, that titer can be lethal. Variations above that point do not seem to produce any consistent variation in the fetal outcome. A titer that starts out at 1:256 and is "brought down" to 1:8 by any means whatever should not be cause for optimism about the final outcome for the baby. A drop to a low level in the last six weeks of pregnancy should not be taken as a favorable sign.

In none of our severely sensitized women was there any instance of major group incompatibility for the husband's red cells. The importance of ABO incompatibility as a protective mechanism has been frequently mentioned.^{19, 20, 21, 22}

Rh hapten made in our own laboratory and by a commercial pharmaceutical house was not effective in eliminating anti-Rh antibodies from the peripheral blood of pregnant or nonpregnant Rh-negative sensitized women when used as herein reported. We believe any drops in titers were coincidental, such as occurred in the last case. Cases 1, 3, and 4 were admittedly treated too late in pregnancy to expect good results. But the negative results in the nonpregnant patients give rise to grave doubts of its value during pregnancy. Our failures may be a matter of dosage and/or potency. However, larger doses than here employed might be financially prohibitive, or, if used very early in pregnancy, the amount required would seriously limit the number who could be treated.

Conclusions

1. In the dosage used, Rh hapten, made in our own laboratories, and by one of the pharmaceutical houses, did not produce a negative Rh antibody titer in pregnant or nonpregnant sensitized Rh-negative women.
2. Hapten did not appear to influence favorably the baby's survival rate.
3. Certain limitations in the interpretations to be made from antibody titers were emphasized.

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In-patients were treated at St. Mary's and De Paul Hospitals, St. Louis.

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CONSERVATIVE THERAPY IN LOWER NEPHRON NEPHROSIS

Report of Two Cases With Survival

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THE etiology of lower nephron nephrosis and of its consequence, acute renal insufficiency, is extremely diverse. A number of reports review the occurrence, pathology, and clinical description of renal shutdown of this type.^{1-8, 21-22} Because of the not uncommon association of lower nephron nephrosis with certain complications of pregnancy, its management has become a therapeutic problem of special interest to the obstetrician.

Strauss⁶ has critically considered the methods proposed for the treatment of the anuric phase of this condition and has questioned the value of such procedures as renal capsulotomy, splanchnic block, x-ray irradiation of the kidneys, and spinal anesthesia in speeding spontaneous diuresis. The "self-limited" nature of the pathologic process has been emphasized by Thorn²² who advocates a regime of fluid restriction, glucose administration, and indicated supportive measures during renal shutdown, and active replacement of electrolyte and water once diuresis is established. Such management is consistent with the views expressed by a number of authors^{2, 4-6, 8-12, 21} and with the experience of this Department.¹³ The therapy employed in the following cases is illustrative of this conservatism.

CASE 1.—The patient, a 24-year-old white primigravida, entered another hospital in the nineteenth week of gestation because of threatened abortion. Several hours following admission the fetus was expelled but, due to hemorrhage and retention of the placenta, a curettage was performed. Considerable bleeding attended this procedure and a transfusion of Type A, Rh-positive blood was given. After receiving approximately 300 ml. of this blood the patient reacted with a severe chill and became cyanotic. Response to supportive treatment including oxygen was equivocal, the blood pressure remaining at shock or preshock levels for the ensuing eighteen hours during which time bleeding continued in spite of intrauterine packing. Additional transfusions of Type A blood amounting to 1,150 ml. were given during this period together with 500 ml. plasma and 1,000 ml. of 5 per cent dextrose in water. No further transfusion reaction was noted, but following the administration of these fluids the patient developed pulmonary edema which responded satisfactorily to digitalization and oxygen.

After the initial transfusion, only small amounts of reddish urine were obtained by catheter. On the third day of her illness the patient received 1,750 ml. of M/6 sodium lactate solution and was transferred to this hospital for treatment of anuria.

On admission the patient appeared to be a well-nourished and well-developed young woman, rather drowsy, reacting somewhat sluggishly, but well oriented in time and space. Her only complaints were mild nausea, singultus, and blurring of vision. Blood pressure was

110 systolic, 72 diastolic, temperature 98.2° F., pulse 80, and respirations 20. A Grade 3 coarse systolic murmur was heard over the precordium (a history of rheumatic fever at age 12 years was obtained). The feet and ankles appeared swollen but did not pit on digital pressure. Laboratory examination showed the hemoglobin concentration to be 4.5 Gm. per cent; erythrocyte count 1.8 million; hematocrit 14 volumes per cent, and the white count 24,550 with 84 per cent polymorphonuclear leucocytes. The blood nonprotein nitrogen concentration was 87 mg. per cent and the serum carbon-dioxide combining power 18.5 mEq. per liter.* The output of urine was insignificant. The patient's blood was typed and found to be *Type O, Rh positive*.

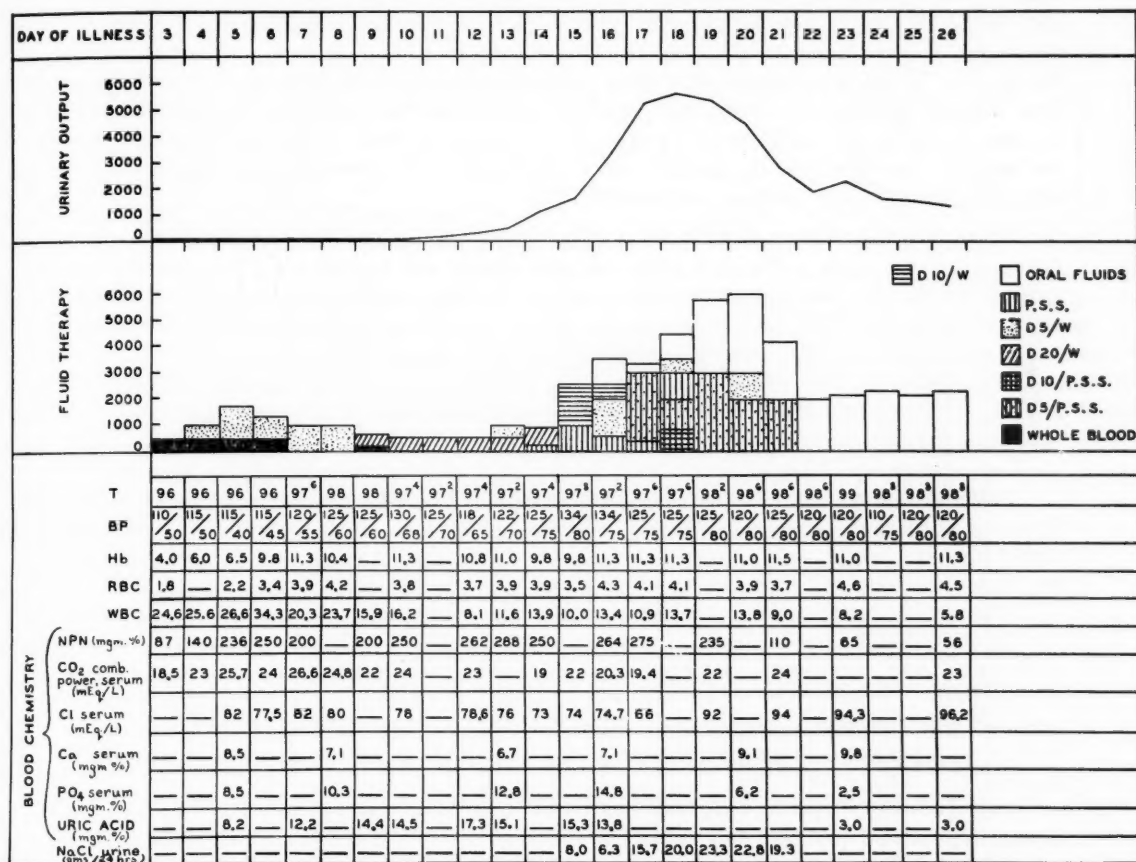


Fig. 1 (Case 1).—Lower nephron nephrosis.

Initial treatment was directed at correction of the marked anemia by the cautious administration of whole-blood transfusions, the patient being carefully observed for signs of excessive hydration. As persistent nausea precluded oral feeding until the nineteenth day of her illness, the patient was maintained on limited amounts of parenteral glucose solutions with vitamin supplements. With the establishment of diuresis there was marked improvement in gastric intolerance and fluids were taken freely by mouth.

On admission the patient received 0.1 mg. digitoxin for maintenance of previous digitalization. Seventeen hours later the pulse became grossly irregular and an electrocardio-

*mEq./L may be converted to other units of concentration by the following factors: mEq./L chloride \times 5.6 equals mg. % NaCl. mEq./L carbon dioxide \times 2.2 equals volumes per cent.

gram showed A-V nodal rhythm with complete auriculoventricular block. A mitral diastolic murmur was heard at this time. Varying degrees of heart block persisted during the following 10 days with gradual return to normal conduction and rhythm.

With the occurrence of hypocalcemia, calcium gluconate was given empirically in small amounts, and, following the development of a mild hemorrhagic tendency on the seventeenth day, the patient also received vitamin K. No clinical effect was observed with either substance. The prothrombin time was normal.

Except for occasional mild puffiness of the face, the patient remained free of edema and no signs or symptoms of pulmonary congestion occurred. Until diuresis was well developed the patient's sensorium remained clouded and varying degrees of disorientation were present. Mild twitching movements of arm and leg muscles were noted between the ninth and thirteenth day in association with generalized mild pruritus. Spontaneous increase in the output of urine began on the eleventh day and increased to a maximum on the eighteenth. During this period replacement of sodium chloride losses and maintenance of fluid balance were actively undertaken. Subsequent recovery was uneventful. Renal function as estimated by urea clearance was found to be 73 per cent of normal 21 weeks following discharge from the hospital. At this time the patient was asymptomatic and appeared well. In Fig. 1 are tabulated the laboratory findings and accessory data.

CASE 2.—The patient, a 38-year-old white multipara, was transferred to this hospital for treatment of shock and anuria after cesarean section and hysterectomy. At the time of delivery the patient was transfused with 1,500 ml. of Type O, Rh-positive blood, following which she developed chills and fever and the output of urine abruptly diminished. Examination of the newborn infant revealed definite evidence of erythroblastosis.

The patient's past history was significant in that she had received a transfusion of 500 ml. of Rh-positive blood approximately eleven months prior to her present illness.

On admission to this hospital moderate hemorrhagic shock and signs of intra-abdominal bleeding were present. The patient's blood was re-typed and found to be Type O, Rh-negative.

Notwithstanding repeated transfusions of compatible blood during the twelve-hour period following admission, the blood pressure failed to stabilize at normal levels and abdominal exploration was carried out. Approximately 2,000 ml. of blood and clots were removed from the peritoneal cavity and secondary suture of bleeding points was effected.

The patient's immediate postoperative condition was poor, moderate shock persisting for approximately eighteen hours. During this period whole blood was administered almost continuously and because of paralytic ileus and abdominal distention, Wangensteen suction was instituted. Twenty-four hours following operation, the patient's condition was somewhat improved with the blood pressure stabilized at 120/80. At this time the temperature rose to 103° F. and penicillin-streptomycin therapy was started. The output of urine remained insignificant.

On the second postoperative day the blood nonprotein nitrogen concentration had increased to 158 mg. per cent, and, although the sensorium remained fairly clear, the patient showed signs of uremia, including singultus, twitching movements of arms and legs, and pruritus. Examination of the chest revealed dullness over the left lower lobe with scattered crepitant râles and diminished breath sounds. X-ray examination showed a "nonspecific pulmonary infiltration" consistent with "hypostatic pneumonia." Antibiotic treatment was continued, and the patient was maintained on limited amounts of parenteral glucose solutions.

With increasing azotemia, progressive stupor developed, and by the seventh day of her illness the patient was deeply comatose. The serum potassium concentration increased to 7.4 mEq. per liter on the ninth day and electrocardiograms showed changes consistent with potassium cardiotoxicity. Marked acidosis developed on the eleventh day with the serum carbon-dioxide combining power decreasing to 11.3 mEq. per liter. Prompt administration of sodium lactate resulted in rapid clinical improvement.

With the possibility of injury to the lower urinary tract in mind, indwelling ureteral catheters were placed on the sixth day of the patient's illness and urine was excreted in very small amounts from the left kidney on the eighth day. The right kidney began to function

approximately forty-eight hours later. The output of urine gradually increased to over 5 liters per twenty-four hours by the fourteenth day. At this time examination of the chest revealed no evidence of pneumonitis.

With the onset of diuresis, the serum potassium concentration decreased and the electrocardiographic abnormalities disappeared. Blood chemical determinations showed a gradual return toward normal values. The patient's sensorium finally became clear on the eighteenth day of her illness and oral feedings were undertaken in amounts limited by gastric intolerance to food as well as by discomfort occasioned by concurrent stomatitis and esophagitis. Serum chlorides were maintained at or near normal values by prompt replacement of sodium chloride losses attending diuresis. Persistent hypochromic anemia was treated by transfusions of whole blood. The patient was discharged home for further convalescence on the thirty-second hospital day. In Fig. 2 are shown the laboratory findings and other pertinent data.

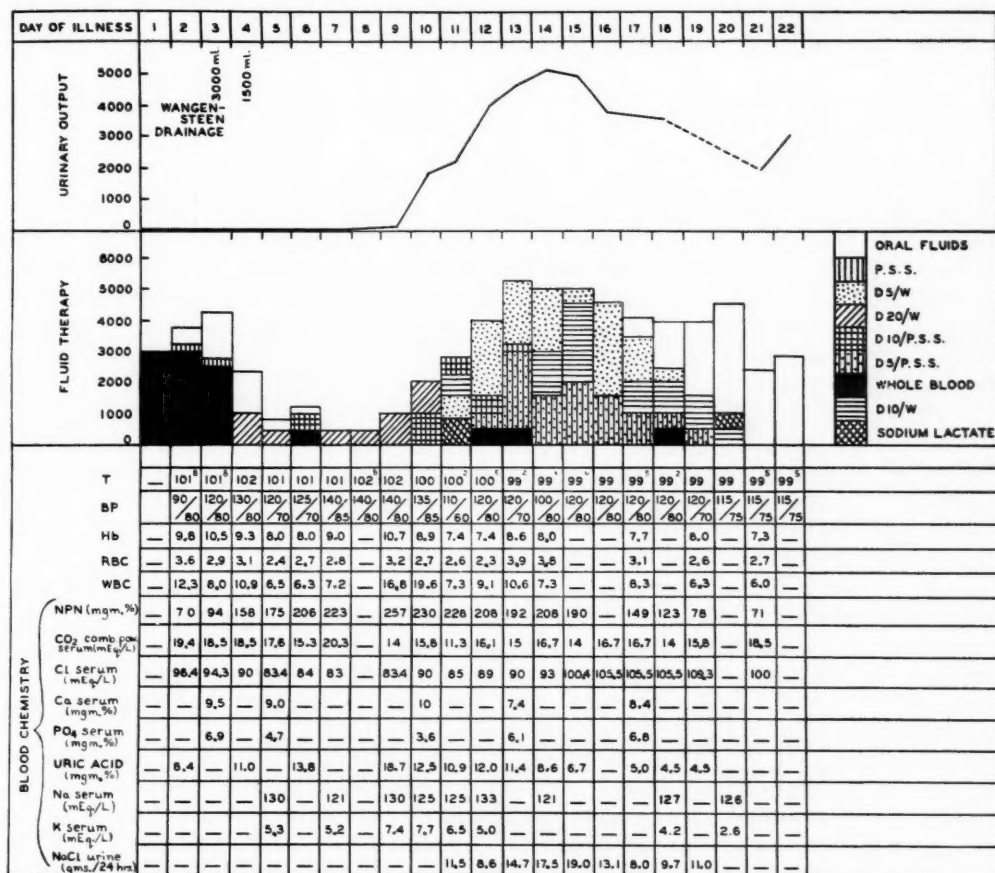


Fig. 2 (Case 2).—Lower nephron nephrosis.

Comment

The clinical course of patients surviving lower nephron nephrosis may be conveniently divided into three periods: (1) The acute phase of anuria following injury to the kidney when the urinary output is less than 100 ml. per 24 hours; (2) A succeeding period of profound diuresis when the 24-hour urine volume may be greater than 5 liters. (3) A convalescent period of variable duration during which the recovery of renal function is more or less complete. Each phase in this sequence is physiologically and chemically unique with

specific therapeutic requirements. At the onset of anuria complicating factors requiring immediate treatment, such as shock due to acute blood loss, may be present as in the cases we have reported.

Once anuria is established, elimination of water from the body is principally by insensible losses from the skin and respiratory surfaces. Under normal conditions such losses are estimated at 1,000 to 1,500 ml. daily.¹⁴⁻¹⁶ It is obvious that administration of fluids in excess of amounts lost through extrarenal channels will result in overhydration, ultimately in cardiac failure. The "forcing" of fluids in the hope of promoting diuresis after extensive kidney injury has been sustained is physiologically unsound. In this connection it is of interest that pulmonary edema is not uncommonly found at autopsy.^{1, 3, 6, 12} Fluid must be restricted to replacement of estimated water losses, one liter daily probably representing the maximum requirement in the absence of vomiting¹⁶ although even smaller quantities have been successfully employed.^{6, 9}

Glucose administration is undoubtedly of value by virtue of its well-known "protein sparing" and ketolytic actions,¹⁷ but it is questionable to what extent excessive protein catabolism¹⁸ resulting from antecedent injury can be inhibited by this means. Although 100-200 Gm. of glucose daily permits a considerable caloric deficit, such amounts may be conveniently given for maintenance of the patient until recovery of renal function occurs. Vitamin supplements of the B complex and ascorbic acid may be added to the parenteral glucose solutions. Thorn²² has recommended the addition of small amounts of plasma to the parenteral glucose in view of possibly suppressing to a certain extent the breakdown of tissue proteins and limiting losses of fluids to the extravascular spaces.

Physiological saline solution administered in amounts of approximately 700 ml. daily have been used by Kugel⁹ during the period of renal shutdown. Probably, however, the use of parenteral saline should be reserved for replacement of sodium and chloride losses from the gastrointestinal tract. Such electrolyte therapy as indicated by Peters²⁵ must be carefully controlled by determinations of the blood chemical pattern.

As shown by the experiments of Atchley and Benedict,¹⁹ acute renal failure is attended by profound readjustments of acid-base equilibria. At the present time adequate data concerning such changes in man are not available but are indicated by our findings (Figs. 1 and 2) and by those of other authors.^{6, 8, 20, 24, 25} Although total base may not be markedly altered, increase in "undetermined acids" is frequently associated with hypochloremia, and as Peters has shown, the changes in electrolyte pattern of the serum may be as diverse as in diabetic acidosis.²⁵ Therapy must thus be individualized as indicated by the chemical changes in the blood, but with special care to avoid excessive hydration of the patient.

It is apparent from reference to Figs. 1 and 2 that considerable deviation from the normal range of electrolyte concentrations occurred in our cases. Complete correction of the chemical disturbances was not obtained nor was this the primary object of our management. The extent to which such readjustment is possible without hazard is difficult to ascertain at the present time. Accordingly, we have been concerned with the correction of the larger changes in pattern, but with due regard for the clinical condition of the patient.

With the establishment of diuresis, the error in renal control of water and electrolyte may lead to the rapid development of dehydration and hypochloremia. Reference to Fig. 1 indicates that, for Case 1, maximum daily losses in the urine in excess of 20 Gm. sodium chloride and 5 L. of water oc-

curred. Comparable losses were incurred by Case 2 of this report. Thorn²² suggests that the secondary peak in mortality occurring about the tenth day following renal shutdown may be accountable on this basis. Parenteral replacement of sodium chloride must be actively instituted at this time in amounts equivalent to urinary losses. Determinations on 24-hour urine collections are satisfactory although at the height of diuresis more frequent analyses are desirable, due to the rapidity of salt depletion. In contrast to that in the period of renal shutdown, there is little danger from administration of large amounts of fluid.

Potassium metabolism in renal insufficiency has been reviewed by Bradley²³ and by Elkinton and associates,²⁴ the latter authors suggesting caution in the acceptance of the various measures that have been proposed for the treatment of hyperkalemia complicating renal failure. The recently described technique of Maluf²⁵ involving perfusion of the small intestine with sodium sulfate solution is perhaps applicable to the control of serum potassium levels, but proper evaluation must await further clinical trial. At the present time, incomplete understanding of electrolyte exchange in acute renal insufficiency makes definitive therapy somewhat problematical. In Case 1 there was no evidence of potassium cardiotoxicity as daily electrocardiograms failed to disclose the characteristic changes described for this condition.²⁴ One serum-potassium determination made on the sixth day of the patient's illness was within normal limits. In Case 2 hyperpotassemia occurred and was associated with changes in the electrocardiogram consistent with potassium cardiotoxicity.

A number of factors undoubtedly contributed to the development of the cardiac irregularity observed on the fourth day in Case 1 (electrolyte disturbance, myocardial injury secondary to prolonged shock, rapid accumulation of metabolic products, residual rheumatic injury, etc.). Digitalis intoxication, however, cannot be excluded. Our experience indicates that when digitalis is administered in association with renal shutdown, initial digitalization and subsequent maintenance should be undertaken with extreme caution.

Summary

1. Two cases of the lower nephron syndrome secondary to hemolytic transfusion reaction and shock are reported.
2. Conservative therapy with special reference to restriction of fluids during acute renal insufficiency is discussed.
3. It is emphasized that corrective electrolyte therapy must be individualized and effected with caution.

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A COMPARATIVE STUDY OF CHEMICAL TESTS FOR THE EARLY DIAGNOSIS OF PREGNANCY, INCLUDING A NEW COLORIMETRIC DETERMINATION

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THE object of this comparative study of chemical tests, including the author's colorimetric determination, was to find a simple, quick, accurate, and inexpensive test for the early diagnosis of pregnancy.

The missed menstrual period has long been a subject of great interest, and always raises the question whether it is due to pregnancy, a pathological condition, or is simply delayed.

There is a variety of chemical procedures for the diagnosis of early pregnancy, many of which have been abandoned. In addition to the well-established biological tests, four new chemical tests have been developed: the Richardson,¹ the Mack-Parks,² the Carson-Saeks,³ and the author's modification of the Richardson test.⁴

Richardson's color test is designed to demonstrate increased titers of free estrone in human pregnancy urine. The coupling of estrone as sodium dinitrophenylhydrazone of estrone is sufficiently accurate to permit the detection of increased amounts of free estrone in the urine of pregnant women.

The Mack-Parks test depends upon the formation of a macroscopic, white precipitate of unpurified pregnandiol in the urine of women during the post-ovulatory phase of the normal menstrual cycle and during normal pregnancy. Mack and Parks state that the presence of pregnandiol in the urine gives presumptive evidence of pregnancy only when the urine is obtained during periods of amenorrhea in women with otherwise normal menstrual cycles.

The Carson-Saeks test is a rapid and simple chemical color reaction for histidinuria based on Voge's⁵ observation that histidine is present in the urine of normal pregnant women. Most of these reports were stimulated by the work of Kapeller-Adler and Herrmann,⁶ who improved Knoop's bromination reaction for urinary histidine and urged its employment as a chemical test for pregnancy.

In the search for a simple, quick, accurate, and inexpensive test for pregnancy, the author modified the Richardson color test. In the use of this original method of reading the color reaction of estrone with the unaided eye, it was sometimes difficult to differentiate urine specimens giving weakly positive or negative reactions. The additional use of the electrophotometer and changes in technique have circumvented interference from nonspecific urinary chromogens, polymerization and oxidation of the dinitrophenylhydrazine reagent, and inaccurate interpretation of varying shades of brown.

Technique

Richardson Test.—The urine is alkalized with half-normal sodium hydroxide solution and extracted with technical chloroform. Following acidifica-

tion with sulfuric acid, an alcoholic solution of dinitrophenylhydrazine is added to the specimen. The solution is allowed to stand twelve minutes and is then realkalinized with an excess of half-normal sodium hydroxide solution. In normal pregnancy urines, the brown color (read grossly) persists after two minutes.

Mack-Parks Test.—This method consists essentially of the extraction with toluene of the acid-hydrolyzed pregnandiol complex of urine, followed by the precipitation of impure pregnandiol.

Carson-Saeks Test.—This method consists of: (1) dilution of the specimen with water to the proper specific gravity, (2) removal of interfering phosphates, nitrites, and solids, and (3) detection of histidine by Knoop's method.

Author's Modification of the Richardson Test.—Alkalinize 4 c.c. of the first morning specimen of urine* in a test tube of convenient size with 4 drops of half-normal sodium hydroxide solution. Add 9 c.c. of technical chloroform, and shake vigorously for one minute. Allow the mixture to stand for one minute or until a clear separation has occurred. Separate the upper clear layer of urine. Transfer this urine to a photometric cell and add 10 drops of half-normal sulfuric acid and 10 drops of 0.1 per cent alcoholic (95 per cent) solution of 2,4 dinitrophenylhydrazine. Allow the solution to stand twelve minutes undisturbed. After this period of coupling, add 2 c.c. of half-normal sodium hydroxide solution, and immediately place the cell in a centrifuge. Alkalinization at this point changes the yellow color of 2,4 dinitrophenylhydrazone of estrone in acid solution to a dark brown. A crystalline or colloid precipitate is produced with this final alkalinization. This precipitate will tend to prevent light transmission in any type of photoelectric colorimeter and will, therefore, be read as color. Centrifuge sample for two minutes at 3,600 r.p.m. Place the cell in the electrophotometer, and read with a blue filter (wave length: 475 mu.†). All urines give a brown reaction upon the second addition of sodium hydroxide solution, but only in urines positive for free estrone will the color remain after two minutes when the meter reading is less than 27.

The author's modification differs from Richardson's procedure as follows:

1. Realkalinization is effected with half the amount of sodium hydroxide solution to prevent dilution of the color.
2. The interfering precipitate is removed from the specimen by centrifugation prior to electrophotometric determinations.
3. The color is read in the electrophotometer with a filter wave length of 475 mu.
4. First morning urine specimens only were used in this study.
5. Urine specimens over three days old and dinitrophenylhydrazine solutions over one week old are not used.

Results

More than 1,900 determinations on 597 women in the childbearing and menopausal periods were made by these four chemical procedures. Of these determinations, 512 were made by the Richardson procedure for free estrone, 242 by the Mack-Parks pregnandiol precipitation procedure, 203 by the Carson-Saeks procedure for histidinuria, and 944 by the author's colorimetric procedure for free estrone. All urine specimens were obtained from private patients of our staff physicians, who verified the results clinically, and all tests were performed by the author.

*The value of the first morning specimen to be published in future work.

†The Leitz photoelectric colorimeter was used throughout this work.

The results shown in Table I indicate that the Richardson estrone test was correct in 94 per cent, the Mack-Parks pregnandiol test in 93 per cent, the Carson-Saeks histidine test in 90 per cent, and the electrophotometric test in 97 per cent of clinically positive cases. The author's test was equally accurate for a control group of normal, nonpregnant, unmarried women of childbearing age, while the next most accurate test was correct in 93 per cent.

TABLE I. A COMPARATIVE STUDY OF CHEMICAL TESTS FOR THE EARLY DIAGNOSIS OF PREGNANCY. SUMMARY OF DATA OBTAINED FROM NORMAL CONTROL WOMEN UNDER 38 YEARS OF AGE

CLINICAL FINDING	RICHARDSON TECHNIQUE		MACK-PARKS TECHNIQUE		CARSON-SAEKS TECHNIQUE		COLORIMETER TECHNIQUE	
	COR- RECT	INCOR- RECT	COR- RECT	INCOR- RECT	COR- RECT	INCOR- RECT	COR- RECT	INCOR- RECT
Pregnant								
a. Less than 1 month	46	4	46	4	45	5	48	2
b. 1 to 3 months	142	8	47	3	45	5	146	4
Nonpregnant	186	14	46	4	43	7	196	4
Total cases	374	26	139	11	133	17	390	01
Per cent	93.5		92.7		88.7		97.5	

In the problem cases of lactation amenorrhea, infrequent bleeding, ectopic pregnancy, pseudocyesis, hydatidiform mole, missed abortion, and symmetrical uterine enlargement (Table II), the Richardson estrone test was correct in 91.7 per cent, the Mack-Parks pregnandiol test in 91.7 per cent, the Carson-Saeks histidine test in 88.8 per cent, and the electrophotometric test in 93.3 per cent.

TABLE II. A COMPARATIVE STUDY OF CHEMICAL TESTS FOR THE EARLY DIAGNOSIS OF PREGNANCY. SUMMARY OF DATA ON PROBLEM CASES. WOMEN UNDER 38 YEARS OF AGE

CLINICAL FINDING	RICHARDSON TECHNIQUE		MACK-PARKS TECHNIQUE		CARSON-SAEKS TECHNIQUE		COLORIMETER TECHNIQUE	
	COR- RECT	INCOR- RECT	COR- RECT	INCOR- RECT	COR- RECT	INCOR- RECT	COR- RECT	INCOR- RECT
<i>Pregnant—Amenorrhea:</i>								
1 week or less	3	0	3	0	0	0	3	0
1-4 weeks	14	2	14	2	4	1	15	1
4-8 weeks	11	0	11	0	12	2	11	0
Over 8 weeks	7	1	7	1	10	0	7	1
Unknown	3	0	3	0	0	0	3	0
<i>Nonpregnant—Amenor- rhea:</i>								
1 week or less	3	0	3	0	0	1	3	0
1-4 weeks	6	1	6	1	10	1	6	1
4-8 weeks	2	0	2	0	11	1	2	0
Over 8 weeks	6	1	6	1	0	0	6	1
Total cases	55	5	55	5	47	6	56	4
Per cent	91.7		91.7		88.8		93.3	

The greatest error occurred in the premenopausal group of women over 38 years of age (Table III). In 20 normally menstruating women, the Richardson and electrophotometric tests for urinary estrone were correct in 85 and 90 per cent, respectively. Twenty nonpregnant women with menstrual irregularities gave correct estrone results in only 85 per cent, while in 6 cases of pregnant women over 38 years of age, the accuracy was 100 per cent. In 6 women with

pelvic tumors, the Richardson and electrophotometric tests were correct in 82.7 and 88.5 per cent, respectively. Age played no significant role in the accuracy of the histidine and pregnandiol tests.

TABLE III. A COMPARATIVE STUDY OF THE RICHARDSON TEST WITH THE AUTHOR'S COLORIMETRIC MODIFICATION. SUMMARY OF DATA OBTAINED FROM PREMENOPAUSAL PATIENTS OVER 38 YEARS OF AGE

	RICHARDSON'S TECHNIQUE			COLORIMETRIC TECHNIQUE		
	CORRECT	INCORRECT	PER CENT CORRECT	CORRECT	INCORRECT	PER CENT CORRECT
Normal menstruating women	17	3	85	18	2	90
Women with irregular menses	17	3	85	17	3	85
Intra-uterine pregnancy	6	0	100	6	0	100
Pelvic tumors:						
a. Endometriosis	1	0	100	1	0	100
b. Ovarian carcinoma	0	1	0	0	1	0
c. Fibromyomata uteri	2	2	50	4	0	100
Total	43		82.7	46		88.5

Browne, Henry, and Venning⁷ obtained low estrogen values in the urine of women who subsequently aborted. A significant degree of correlation exists between the pregnandiol precipitation test, the electrophotometric assay of free urinary estrone, and the clinical course of patients threatening to abort (Table IV). Of 32 patients with bleeding in early pregnancy, 24 aborted. In 19 of those who aborted, the termination of pregnancy was preceded by one or more negative estrone tests, an accuracy of 79.2 per cent. Twenty-three of those who aborted had negative pregnandiol tests before pregnancy termination, an accuracy of 96 per cent. In 10, the tests were negative for free estrone and pregnandiol and remained negative until abortion.

TABLE IV. A COMPARATIVE STUDY OF THE MACK-PARKS TEST WITH THE AUTHOR'S COLORIMETRIC MODIFICATION OF THE RICHARDSON TEST. SUMMARY OF DATA ON PATIENTS WITH THREATENED ABORTION

	MACK-PARKS TECHNIQUE			COLORIMETER TECHNIQUE		
	CORRECT	INCORRECT	PER CENT CORRECT	CORRECT	INCORRECT	PER CENT CORRECT
Threatened abortion terminating in actual abortion	23	1	95.8	19	5	79.2
Threatened abortion with retention of pregnancy	8	0	100	8	0	100
Total	31		96.9	27		84.4

A 6 per cent increase in false positive reactions with urine specimens over 3 days old and with dinitrophenylhydrazine solutions over one week old is demonstrated in Table V and Table VI, respectively.

TABLE V. THE AUTHOR'S COLORIMETRIC DETERMINATION OF URINARY ESTRONE FOR THE EARLY DIAGNOSIS OF PREGNANCY. SUMMARY OF DATA OBTAINED FROM URINE SPECIMENS OVER THREE DAYS OLD

CLINICAL FINDING	NO. OF CASES	NUMBER		PER CENT CORRECT
		CORRECT	INCORRECT	
Pregnant (first trimester)	100	100	0	100
Nonpregnant	100	92	8	92
Total	200	192	8	96

TABLE VI. THE AUTHOR'S COLORIMETRIC DETERMINATION OF URINARY ESTRONE FOR THE EARLY DIAGNOSIS OF PREGNANCY. SUMMARY OF DATA OBTAINED FROM URINE SPECIMENS USING 2,4 DINITROPHENYLHYDRAZINE SOLUTIONS OVER ONE WEEK OLD

CLINICAL FINDING	NO. OF CASES	NUMBER		PER CENT CORRECT
		CORRECT	INCORRECT	
Pregnant (first trimester)	100	100	0	100
Nonpregnant	100	92	8	92
Total	200	192	8	96

Comment

Evidence presented in this paper shows that the free estrone in human pregnancy urine may be estimated with a high degree of accuracy by means of the electrophotometer. The definite advantages of this procedure are the 4 per cent greater accuracy* and the ease with which the final color can be read in comparison with the Richardson estrone test. The results obtained in 1,901 urinalyses in the cases of 597 women, many of which were problem cases, indicate that it may be used with accuracy as an inexpensive and rapid office procedure for the diagnosis of pregnancy before the thirtieth day of gestation.

The presence of free estrone in this test was confirmed by isolation and characterization of the pure substance by Rapp.⁸ The spectrogram (Fig. 1) of the authentic sample of sodium dinitrophenylhydrazone of estrone compared in all respects with the spectrogram of the hydrazone derivative isolated from the urine.

In problem and normal cases the colorimetric tests, costing but a few cents, can be carried out in less than twenty minutes with an accuracy equal to that of expensive biological tests. While the accuracy of the Aschheim-Zondek and Friedman tests is commonly stated to be 98 per cent, many investigators^{3, 9, 10} have found the incidence of false positives resulting from these tests to be more than 2 per cent.

False positive estrone reactions are produced by compounds with available aldehyde or ketone bodies that are not removed from the urine during the treatment before color formation. Only fresh urine specimens should be used, because bacterial contamination hydrolyzes the fixed estrone, thereby causing an abnormal increase in free estrone, the substance upon which the final color depends. In solution, 2,4 dinitrophenylhydrazine oxidizes alcohol to acetaldehyde, which in turn gives a positive color reaction. To prevent polymerization and oxidation, this solution should be prepared every 72 hours.

The pregnandiol test studied in this laboratory depends upon the precipitation of unpurified pregnandiol from the urine of women during the postovulatory phases of normal menstrual cycles and during amenorrhea of normal pregnancy. The presence of pregnandiol during amenorrhea of normal pregnancy indicates presumably normal corpus luteum and placental function. In this study, all but one woman with spontaneous abortion showed a negative pregnandiol excretion prior to expulsion of the products of conception.

It is evident from the foregoing and from other reports in the literature^{11, 12, 13} that the positive pregnandiol tests should be interpreted with caution, since they give presumptive evidence of pregnancy only when the urine is obtained during periods of amenorrhea in women with otherwise normal menstrual cycles. When these criteria are followed, the accuracy of the pregnandiol test in nonpregnant states compares favorable with its accuracy in normal pregnancy.

*The value of "p" calculated from Chi-square of fourfold table with grand total figures for author's method compared with Richardson's procedure (Table I), is 0.23.

Table IV demonstrates that, in cases of threatened abortion, persistently negative readings with the estrone and pregnandiol tests are of value as a criterion for uterine curettage. Although this series of cases of threatened abortion is small, prediction of the course of pregnancy was made correctly in all but one case on the basis of the pregnandiol precipitation test.

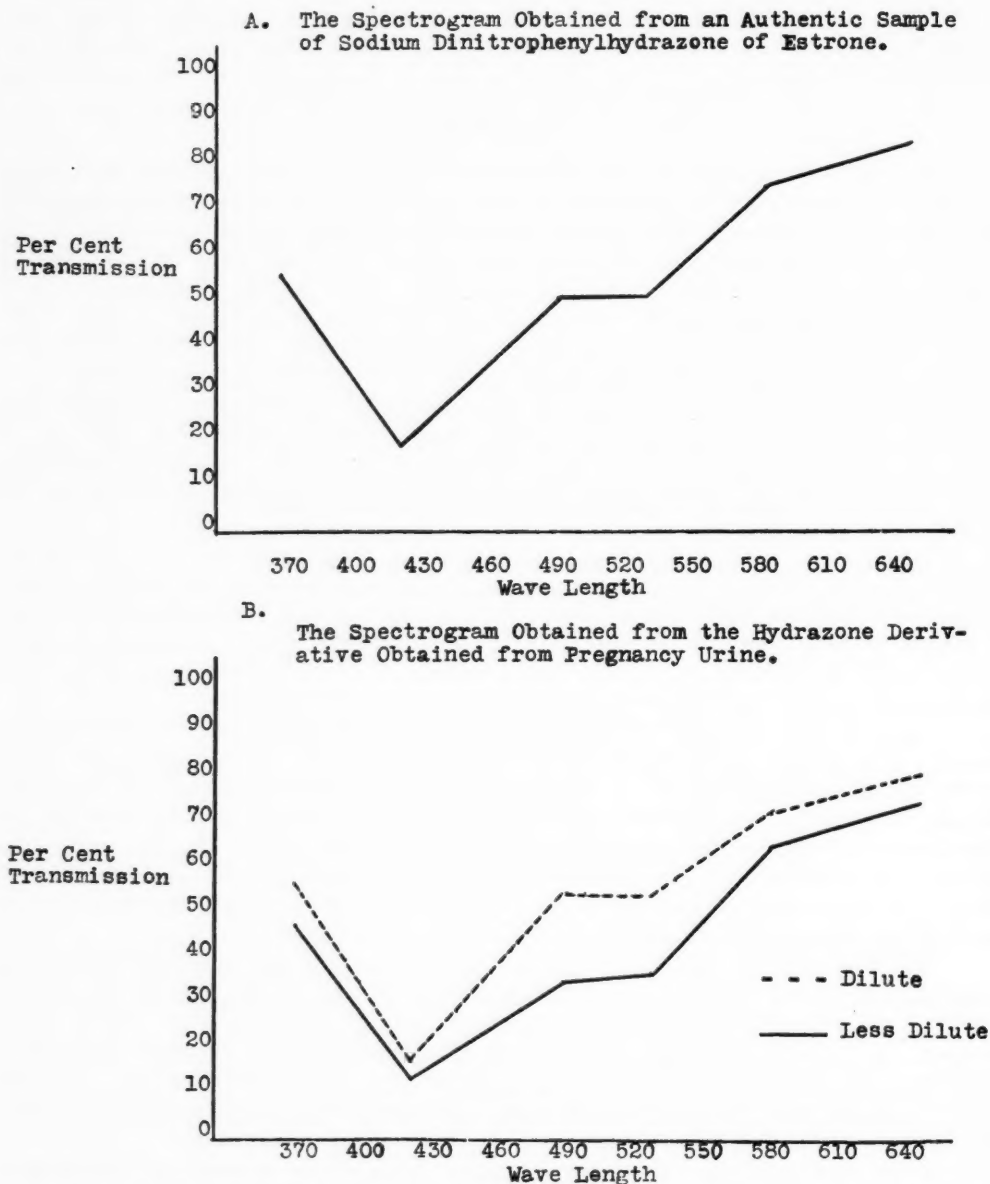


Fig. 1.—The author's colorimetric determination of urinary estrone for the early diagnosis of pregnancy.

Ricketts claims a greater than 94 per cent accuracy for the early diagnosis of pregnancy with the Carson-Saeks test. The author's use of this test gave 88.7 per cent accuracy. Routine qualitative tests can never become an accurate means of diagnosing pregnancy, since, with refinements of technique, almost

all urines become positive for histidine.¹⁴ Because of this margin of error, the test is not of sufficient accuracy for clinical adoption.

Summary and Conclusions

1. A comparative study of four chemical tests for the early diagnosis of pregnancy in the cases of 597 women is presented.
2. A new, simple, quick, accurate, and inexpensive colorimetric determination of free estrone in the urine of pregnant women has been described in detail.
3. The value of the pregnandiol precipitation test and the colorimetric tests in the cases of threatening abortion is demonstrated.
4. Errors in the histidinuria test, rendering it insufficiently accurate for clinical adoption, are given.

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EXTRAPERITONEAL REPAIR OF VESICOVAGINAL FISTULAS*

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THE successful repair of vesicovaginal fistulas is one of the difficult problems which confront the gynecological surgeon. This problem becomes more difficult when one is dealing with high fistulas which commonly follow hysterectomy. The following report presents a series of cases in which the approach has deviated from that in general usage, and can best be described as the extraperitoneal repair of vesicovaginal fistulas.

Fortunately, in modern obstetrical practice, the occurrence of vesical fistulas resulting from trauma and necrosis is relatively rare. Conversely, with the advent of the more radical types of gynecological operations, chiefly, complete hysterectomies, Wertheim operations, and vaginal plastic procedures, the number of postsurgical fistulas has increased. Obstetrical fistulas are generally confined to the lower half of the vagina and can be approached and successfully closed by the vaginal route. Surgical fistulas, on the other hand, usually occur at the apex of the vagina, a most inaccessible position, making the approach difficult, particularly in the absence of the cervix, which normally provides a site for traction and facilitates exposure.

Etiologically, there are three factors which engender this type of surgical fistula. The most common is a puncture of the bladder wall by a suture at the time of operation; next in the order of occurrence is the tissue necrosis due to loss of blood supply resulting from extensive dissection about the bladder; and, finally, direct trauma to the bladder, unrecognized at the time. Fistulas resulting from any one of these three causes usually are found at or near the apex of the residual vagina, and about 1 to 3 cm. above the trigone of the bladder. In this particular location, vaginal repair is difficult and too frequently results in failure. For this reason, other approaches have been essayed with varying degrees of improvement in results.

Today there are in use four generally accepted techniques for the repair of vesicovaginal fistulas:

1. The vaginal approach. This is the procedure of choice in those cases in which the fistula lies accessibly within the lower two-thirds of the vagina. The upper third of the vagina, however, presents increasing difficulties in adequate exposure and mobilization of tissues. Chiefly for this reason, alternate approaches have been sought.

2. The transvesical approach. Employing this method, repair of fistulas not easily accessible through the vagina has been reported in the recent litera-

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ture by Farsht,¹ Phaneuf and Graves,⁴ and Fagerstrom,⁶ who, among others, report successful closures. Most of the papers describing this technique have been submitted by urologists. This appears to be an excellent method for the repair of a limited number of small fistulas, high in the vagina, and not close to the ureteral orifices. When the surgeon is dealing with large defects and fistulas in close proximity to the ureters, the degree of safe mobilization available by the transvesical approach seems insufficient to insure successful closure.

3. Transperitoneal approach. Repair of fistulas high in the vagina through the peritoneal cavity is an approach which affords excellent exposure and a high degree of mobility of the fistulous tract. The danger in this method, as reported by Legueu,² is the risk of peritonitis, either from contamination at the time of operation or from subsequent leakage of urine.

4. Implantation of the ureters into the bowel is sometimes employed in those cases which have not responded successfully to repeated attempts to obtain a closure.

The surgical principles governing the successful repair of vesicovaginal fistulas are: (1) the elimination of infection; (2) good exposure and adequate mobilization; (3) efficient drainage.

No attempt to close a vesicovaginal fistula should be made until the genitourinary tract is proved free from infection. Any pathologic condition responsible for persistent infection must be eradicated. The importance of this principle is illustrated in the following case from this series.

The one failure in this series occurred in a patient who had been operated upon unsuccessfully by the vaginal route on two previous occasions. Urine cultures showed *Escherichia coli*. Cystoscopic examination revealed four wire sutures penetrating the bladder wall. Attached to one of these sutures was a large calculus obscuring the right ureteral orifice. The sutures and the attached calculus were removed at the time of repair of the fistula. The tissue about the right ureteral orifice was red and edematous. Extensive chemotherapy was instituted, but postoperative infection supervened. The patient still shows a small defect in the lower pole of the current repair, near the right ureter. This failure might have been avoided if the calculus and wire sutures had been removed and the urinary-tract infection eliminated before closure of the fistula was attempted.

Good exposure and mobilization of the fistulous tract are essential to successful repair. Fistulous tracts occurring in the lower two-thirds of the vagina present a lesser problem in good exposure, excision of the fistulous tract, and mobilization of the tissues in order that the bladder wall may be approximated without tension. On the other hand, in the case of fistulas located in the upper third of the vagina and particularly in the vault, exposure and adequate mobilization may be exceedingly difficult. In order to obtain satisfactory exposure and mobility, therefore, the fistula must be approached by a different route. The only other approach to such fistulas is suprapubic, either transperitoneally with its attendant risk, or more safely, extraperitoneally.

The most painstaking dissection and repair may be unsuccessful if the postoperative drainage is insufficient. Drainage of the bladder through a urethral catheter alone may be totally inadequate. It may become plugged or partially withdrawn. In this series all bladders have been drained postoperatively by the use of a suprapubic catheter in addition to an indwelling Foley urethral catheter. With this type of double drainage, no difficulty has been experienced with postoperative bladder decompression.

Only two references have been found in the literature pertaining to the extraperitoneal repair of vesicovaginal fistulas. Phaneuf³ mentions this ap-

proach in listing the several techniques for the repair of vesicovaginal fistulas, but does not include a detailed description. Scott and Wilson⁵ describe an extraperitoneal technique of repairing a high ureterovesicovaginal fistula with reimplantation of the ureter into the bladder.

The help of a competent urologist is important for the successful repair of vesicovaginal fistulas, not only in the evaluation of the patient's urinary tract before surgery, but also for his assistance at the time of operation. The initial study of the case calls for a thorough pelvic examination to determine the location and size of the defect. At the same time the state of health of the vaginal and pelvic tissues should be determined. A thin-walled irritated vagina will look vastly improved after stilbestrol therapy. The patient's urinary tract should be thoroughly evaluated. The presence of infection in the bladder should be noted and the size and exact location of the fistulous tract observed cystoscopically. If the fistula is surrounded by granulation tissue, then biopsies should be taken, especially if the fistula occurred after a complete hysterectomy for uterine malignancy. Stones and foreign bodies in the bladder should be removed before any attempt is made to repair the defect. The upper urinary tract should be investigated by intravenous pyelography. Retrograde studies may be done if indicated. Persistent infection of one or both kidneys should be treated before any repair is attempted, even though this may require surgery, as, for example, in the case of coexisting renal calculi.

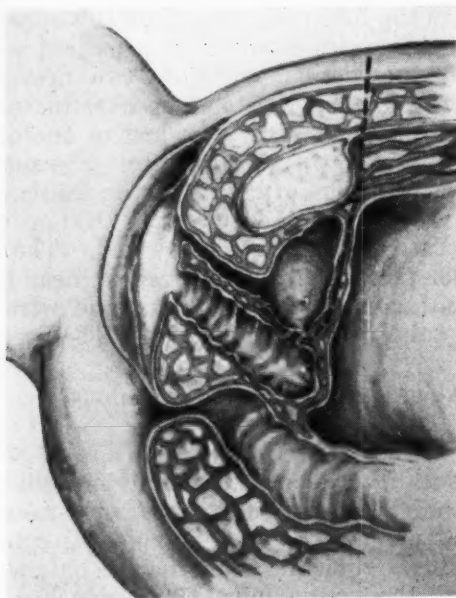


Fig. 1.—Sagittal view of the pelvis showing the extraperitoneal approach to a vesicovaginal fistula. The dissection follows the dotted line between the recti muscles. The peritoneum and fascia are next dissected from the bladder down to the vagina and thence between bladder and vagina around the fistula.

Preoperative Preparation

The urinary tract, vagina, and surrounding tissues are rendered as healthy as possible and free of infection before surgical attack on the fistula is made. The urine must be free from bacteria as determined by urine culture. Prophylactic antimicrobial therapy is started two days before surgery and continued thereafter until the temperature has been normal forty-eight hours. Vaginitis and irritation about the vagina are cleared up by means of sitz baths, stilbestrol,

and acidification of the urine. Anemia, if present, is corrected by indicated therapy. A low-residue, high-protein diet, supplemented by vitamins, is instituted during the preoperative hospital stay. During this time, psychological preparation of the patient is begun to insure her cooperation and acceptance of the two weeks' postoperative prone position.

Description of Operation

The perineum and vagina are prepared with an aqueous solution of Zephiran and the abdomen painted with tincture of Zephiran. Other similar preparations may be used. In some cases the vagina is packed with gauze, which is removed at the time the fistulous opening in the vagina is sutured. This is not an absolute necessity, but may facilitate the dissection. The abdomen is opened either by excising the scar of the previous incision or by a transverse Pfannenstiel type of incision, which is preferable in the obese patient. The abdominal wall is opened down to the transversalis fascia. This fascia is exposed laterally and is incised transversely about two inches above the pubis (Fig. 2).

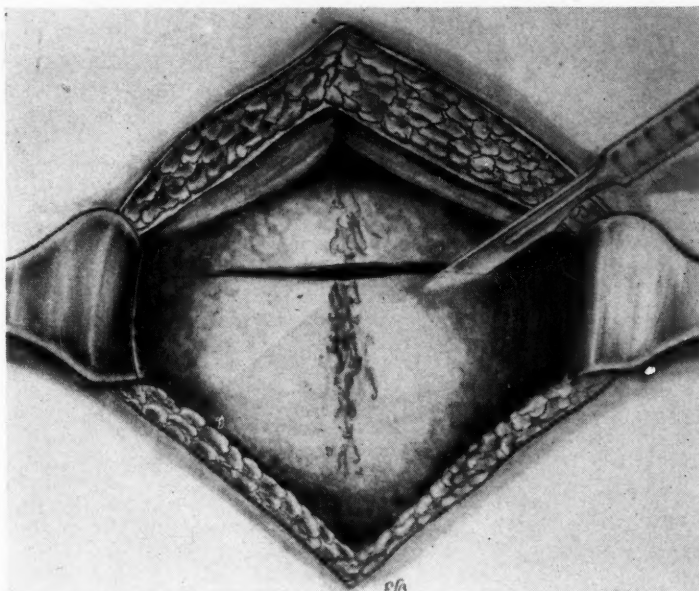


Fig. 2.—The abdominal wall is opened down to the transversalis fascia. This fascia is exposed laterally and is incised transversely about two inches above the pubis. It is then underdissected in all directions.

It is then underdissected in all directions. The fundus of the bladder is picked up and the fatty tissue surrounding the bladder dissected away by sharp and blunt dissection. By means of blunt dissection the lateral walls of the bladder and the lateral peritoneum usually can be freely mobilized down to the vagina. The most difficult part of the dissection involves freeing the peritoneum from its attachment to the fundus of the bladder in the midline (Fig. 3). The firmness of this attachment varies in individuals. In some there is only a small area to separate; in others there may be a large triangular area where the dissection is difficult and the danger of opening the peritoneal cavity is great. In the event the peritoneal cavity is opened, it should be closed immediately. As soon as the vagina is reached, it is grasped either by a T-clamp or an Ochsner clamp to elevate the vagina and maintain traction. The line of cleavage between the

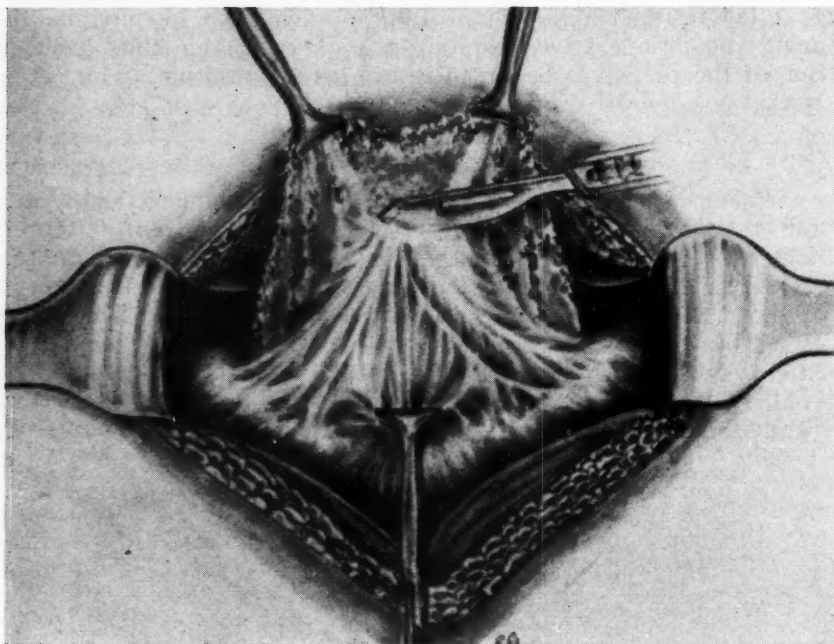


Fig. 3.—The fundus of the bladder is picked up and the fatty tissue surrounding the bladder dissected away. The peritoneum and fascia are then dissected, by sharp dissection, from their firm attachment to the bladder in the midline.

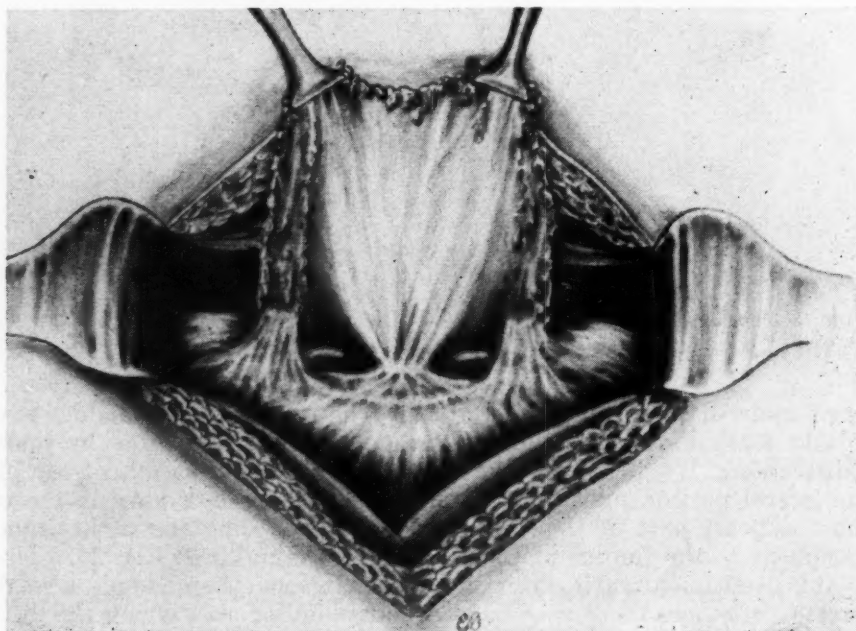


Fig. 4.—The peritoneum has been dissected from the bladder down to the vagina, revealing the fistula in the midline and the ureters on either side.

vagina and the bladder is further developed (Fig. 4). It is then easy to dissect the bladder laterally on either side of the fistula. At this stage of the procedure the bladder is opened and the fistulous tract is explored from above (Fig. 5).

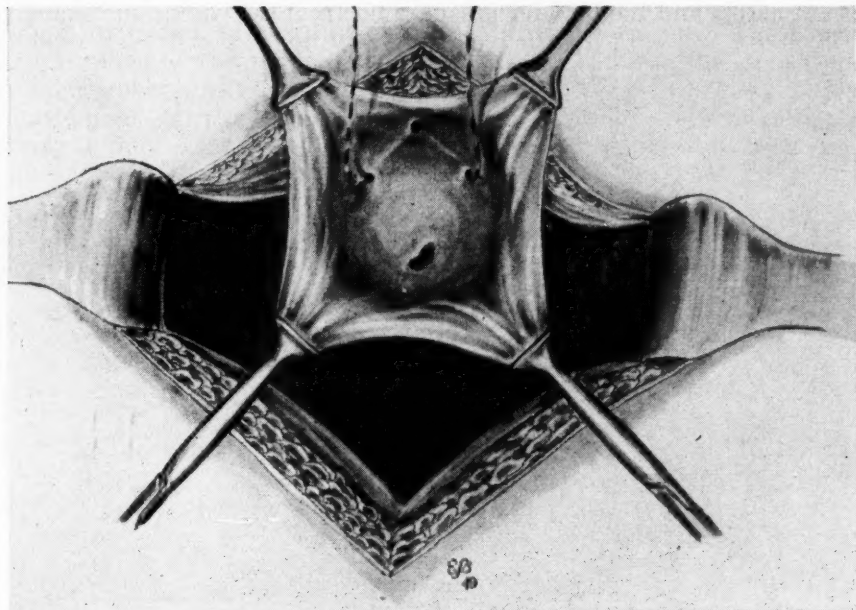


Fig. 5.—The bladder has been opened, revealing the fistula from within, lying high above the ureters. The ureters may be catheterized to facilitate dissection if so desired.

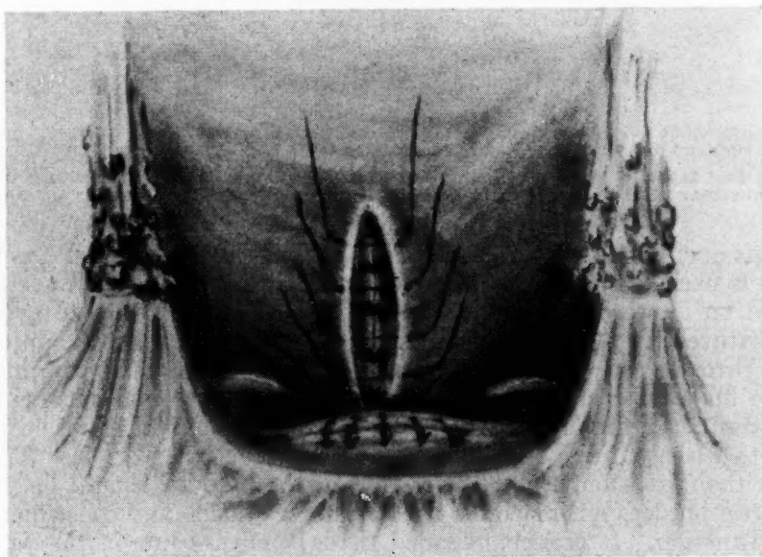


Fig. 6.—The vaginal wall is closed with interrupted sutures, everting the mucous membrane into the vagina. The first layer of sutures has been placed in the bladder and tied. The second layer has been placed. Note the ureters lying lateral to the bladder wound. The bladder is closed at right angles to the vaginal closure.

It is usually advisable to insert a probe through the fistula into the vagina so that the tract can be better visualized when it is incised. The relationship of the ureters to the fistulous opening can be plainly seen. It may be desirable under some circumstances to insert catheters into the ureters. The fistulous tract is cut across and the bladder is separated from the vagina far enough below

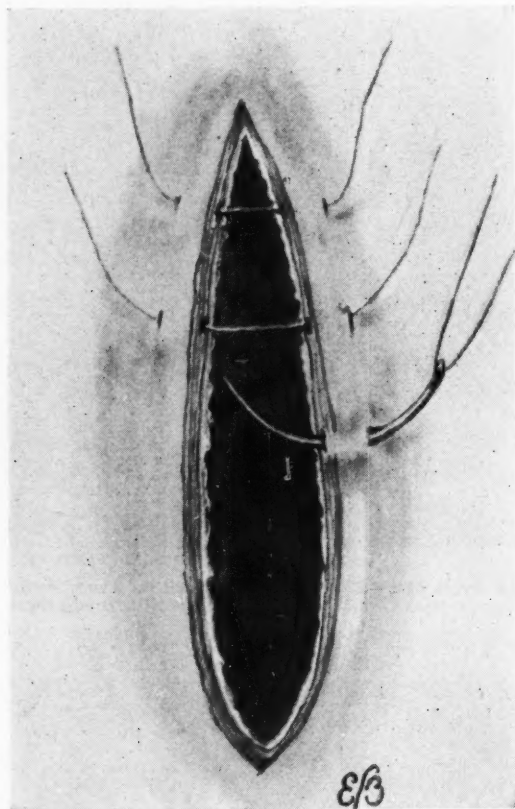


Fig. 7.—The first layer of sutures is being placed in the bladder wall. The suture includes only the muscular wall of the bladder and does not go through the mucous membrane.

the fistulous opening so that a good closure can be made. All scar tissue around the fistula is excised. If the fistula opens near a ureter, then the ureter on that side should be dissected from the surrounding tissues in order to avoid injury when the sutures are placed. The vaginal wall is closed with interrupted sutures of No. 00 chromic catgut (Fig. 6), everting the mucous membrane into the vagina. The bladder is closed in two layers using interrupted sutures of No. 00 chromic catgut, the first layer being placed only through the muscle. It is not advisable to place sutures through the bladder mucosa (Fig. 7). The sutures are tied without tension. The suture line in the bladder should be planned so that its direction does not place the ureters under tension and consequently interfere with function. It is recommended that the suture line in the vaginal wall be placed at right angles to the suture line in the bladder. The danger of the two suture lines approximating each other is minimized since adequate mobilization of the bladder will alter the positions of the vaginal and bladder portions of the fistula relative to each other. After the fistula is closed, the area is carefully inspected for good hemostasis.

A No. 30 Malecot or Pezzer catheter is placed in the bladder suprapubically at an oblique angle. The bladder is then closed around this catheter with sutures of No. 0 chromic catgut (Fig. 8). One Penrose drain is then placed on each side of the bladder and brought out through the lower angle of the incision. These drains are usually removed on the third or fourth postoperative day. The fascia is then approximated with sutures of No. 0 chromic catgut. The suprapubic tube is sutured into the fascia and again into the skin at the upper angle of midline incisions and at the midpoint of transverse incisions. The skin is closed with interrupted sutures of black silk. A No. 24 Foley urethral catheter with a 5 c.c. bag is then passed and left in place after the bladder has been irrigated.

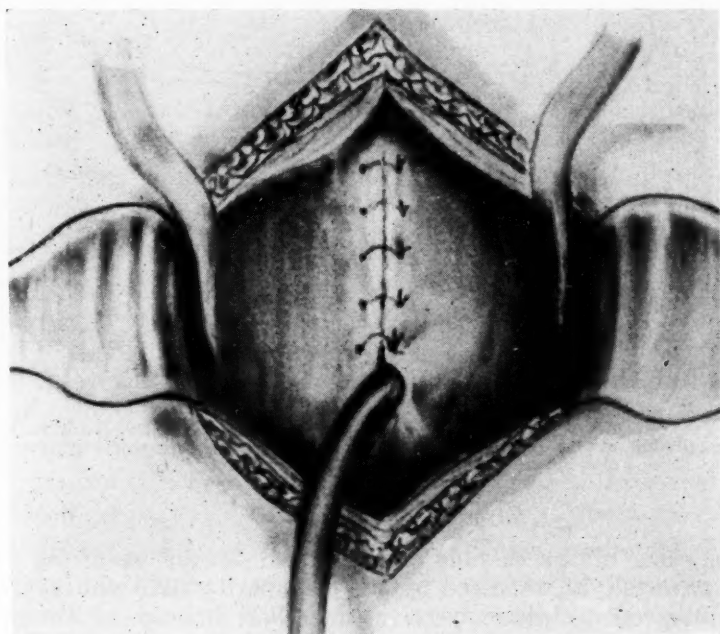


Fig. 8.—The bladder is closed suprapubically at an oblique angle around either a Malecot or Pezzer catheter. A Penrose drain is then placed on each side of the bladder and brought out through the lower angle of the incision.

Postoperative Care

The patient is placed on her abdomen on a modified Bradford frame (Fig. 9) with an opening in it to permit the attachment of the suprapubic catheter to a constant drainage bottle. The patient is maintained in this prone position for eleven to fourteen days, after which time the suprapubic tube is removed and the patient mobilized. Usually within twenty-four hours after the removal of the suprapubic tube there is no further suprapubic drainage of urine. The Foley catheter is allowed to remain in place for an additional forty-eight hours, or until the suprapubic wound has closed. Postoperative bladder irrigation has not been considered necessary. Antimicrobial therapy is continued until the temperature has been normal for forty-eight hours. The patient is kept on a liquid diet supplemented by vitamins until she is mobilized. Bowel movements are prevented during the period of immobilization in the prone position in order to safeguard the position of the catheters and to reduce the possibility of contamination of the vagina with bowel contents.

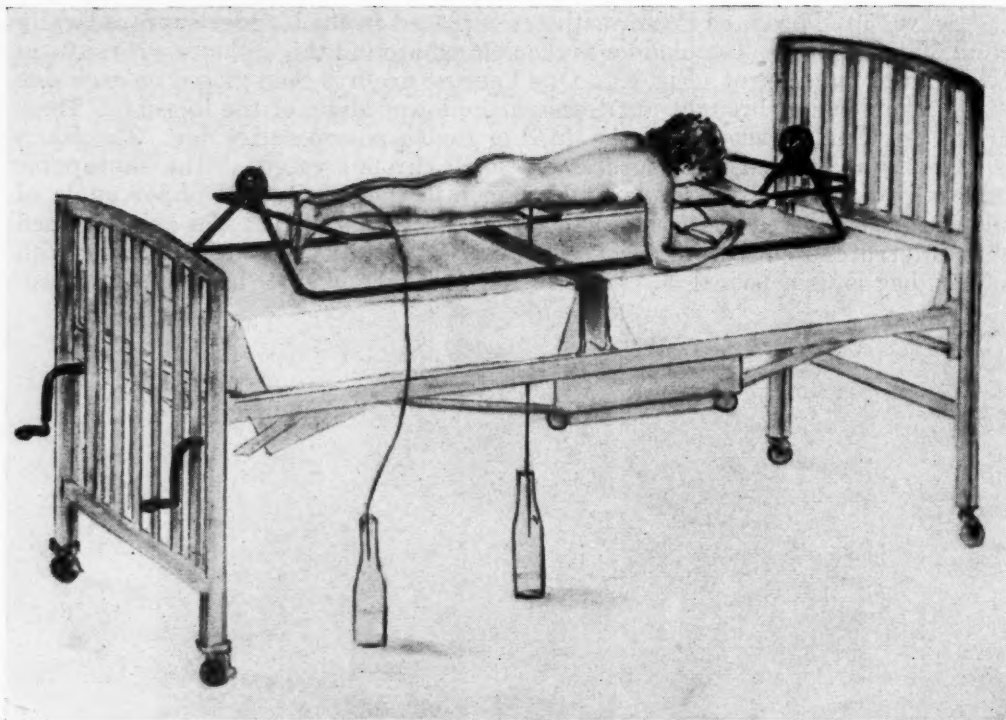


Fig. 9.—The patient is placed on her abdomen on a modified Bradford frame or Stryker frame with an opening in it to permit the attachment of the suprapubic catheter to a constant drainage bottle. The Foley catheter also drains into a bottle.

Summary

Thirteen cases of inaccessible vesicovaginal fistulas resulting from pelvic surgery are reported, all repaired by the extraperitoneal technique. Eleven of these cases followed complete hysterectomies and in each of these the fistula occurred in the scar at the vault of the vagina. One fistula followed supravaginal hysterectomy in which case the fistulous opening was anterior to the remaining cervical stump. One case followed a pelvic infection after hysterectomy. In six cases there had been at least one previous operation to attempt a repair of the fistula by other approaches before the extraperitoneal technique was employed.

The size of the fistulas varied from 0.5 cm. to 5.0 cm. in diameter. The youngest patient was 30 years of age and the oldest was 60. There is one failure in this series. This is believed to have resulted from the fact that the patient had a bladder calculus removed at the time of the repair of the fistula and had a persistent urinary-tract infection.

Note.—There was one death in this series which has come to my attention since presenting this paper. A patient, 56 years of age, died suddenly three weeks after leaving the hospital. The cause of death was undetermined in the absence of an autopsy.

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49 DEERING STREET

**TRICHOMONAS VAGINALIS VAGINITIS:
TREATMENT WITH A NEW SURFACE-ACTIVE TRICHOMONACIDE**

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ALTHOUGH there have been innumerable reports on the treatment of *Trichomonas vaginalis* vaginitis, and dozens of trichomonacides are available for use in this condition, it remains a frequently encountered and difficult problem. As is well known, many therapeutic procedures are time consuming, tedious, and not invariably innocuous; also, recurrence or reinfestation in "cured" cases is more the rule than the exception. We wish, therefore, to report a method of treatment, used during the past year at the Hospital of the University of Maryland, which has given unusually satisfactory results and proved to be exceptionally simple and safe.

Since some of the difficulties of diagnosis and treatment stem from certain misconceptions about trichomonads which have persisted despite convincing evidence of several years' standing, a few of the more pertinent facts about the organism will be briefly reviewed. There are three species of trichomonads which appear to be parasitic to man: *Trichomonas vaginalis*; *Trichomonas tenax*; and *Trichomonas hominis*. These species are so similar that they are difficult to identify positively except by the use of fixed and stained slides. In general, however, *Trichomonas vaginalis* is the largest and is more round in shape than the other two, but its other characteristics are shared by one or both of the other species: it has four anterior flagella, a less-than-body length undulating membrane, accompanied by a very narrow costa with no posterior trailing flagellum. There is a slender accessory filament at the margin of the undulating membrane, and a parabasal apparatus consisting of a fine parabasal fibril with a much thicker parabasal body of different texture (No. 1, Fig. 1).

For many years it was believed that these three species might occur in various parts of the human body, and even that one species might change into another, so that any one of them might be responsible for vaginitis. In recent years, however, it has been incontrovertibly established that they are distinct species, both morphologically and physiologically. *Trichomonas vaginalis* occurs in the genitourinary tract; *Trichomonas tenax*, in the mouth; and *Trichomonas hominis*, in the intestine. Furthermore, the peculiarities of each species make each one adapted to its own environment but unable to survive in the environment which suits the others. It can also bear repeating that the common animal trichomonads are in no way concerned with human infections.^{1 (a)}

Purpose of Study

This study was undertaken to investigate a new trichomonacide, composed of a mixture of two quaternary ammonium compounds (1 per cent) in a vehicle of sodium carboxymethylcellulose (99 per cent). The preparation is marketed under the trade name of Tetronyl.*

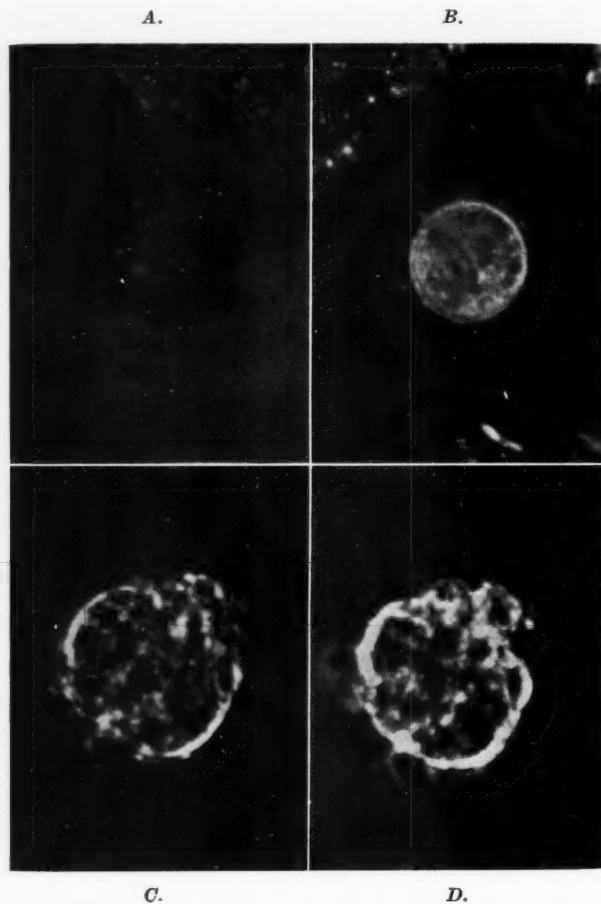


Fig. 1.—Mode of action. ($\times 2,000$.)

A, A living trichomonad, showing three of the flagella.

B, Immediate effect of the trichomonacide, in 1:10,000 dilution—a “balling up” of the organism.

C, Thirty seconds after contact. Note rupturing cell membrane.

D, Same organism 1 minute later; cytoplasmic contents escaping through ruptured cell wall.

Both the quaternaries and the sodium carboxymethylcellulose are surface-active materials. The active ammonium ingredient is a potent and quickly acting trichomonacide; dilutions of 1 in 10,000 kill trichomonads in vitro in less than one minute; 1 in 20,000 kill in less than 3 minutes; 1 in 100,000 kill within 15 minutes.² These quaternary ammonium compounds act on trichomonads in a unique manner. Apparently they make the organism's cell membrane permeable, so that as soon as they come into contact with the mem-

*Tetronyl is a product of Smith, Kline & French Laboratories, Philadelphia, which supplied the materials for this study. The quaternary ammonium compounds in the product are: alkyl [C_8H_{17} to $C_{18}H_{37}$] dimethyl-3,4-dichlorobenzylammonium chloride and alkenyl [$C_{16}H_{31}$ to $C_{20}H_{39}$] dimethylethylammonium bromide.

brane the protozoan starts imbibing fluid from the surrounding medium. After sufficient imbibing and swelling the cell membrane bursts, discharging the cytoplasmic contents of the cell (Fig. 1, C). We can but theorize as to this mechanism of action. Since these quaternaries have fat-emulsifying properties, the lipoid substances present in the membrane of the protozoan may be emulsified, thereby permitting penetration of aqueous materials from the surrounding medium; or, the permeability of the cell membrane may be altered by the surface-active trichomonacide. The results are clearly discernible in vitro.

Tetronyl is different from other trichomonacides in that its action does not in any way depend upon a change in the pH of the vaginal tract; it is effective in a pH range of from 3.2 to 10.0.² It is commonly thought that the artificial lowering of the vaginal pH would serve a useful purpose in the treatment of trichomonad infestations. However, it has now been established^{3, 4, 5, 6, 7} by a number of investigators, namely, Geiger, Mohr, Zener, Lissimore and Currie, and associates, quoted in the exhaustive treatise on *Trichomonas vaginalis* by Ray E. Trussel, 1947, that an acid medium is not inimical to the optimum growth of *T. vaginalis*. The following investigative findings support this belief. Liston and Cruickshank reported that the average vaginal pH in 34 pregnant women with trichomoniasis was 5.5, and Lissimore and Currie found the average pH of the vaginal discharges from 71 infected patients was 5.99. Trussell and MacDougal are in accord with those above noted; they found the pH range was 4.55 to 6.38, with an average of 5.58. Other investigators substantiate these reported observations.

As is well known, the efficiency of many of the medicaments advocated in the treatment of *Trichomonas vaginalis* vaginitis is based on a lowering of the pH of the vaginal secretions, from the belief that a very acid medium is definitely antagonistic to the life and growth of the protozoa. From the reported observations here tabulated, one must feel doubtful that acidity plays a definite role in the eradication of the infection. Since *Trichomonas vaginalis* grows luxuriantly in acid secretions, obviously efforts to maintain an acid pH of the vagina are not of great value.

In addition to its action on trichomonads, Tetronyl has a wide range of bactericidal and protozoacidal effectiveness. It is effective against such other vaginal infective agents as *Monilia albicans* and against many of the bacteria that so often complicate trichomonad infestations.

The sodium carboxymethylcellulose vehicle acts as a dispersing agent which carries the trichomonacide quickly and efficiently into the rugae of the tract, where it clings to the vaginal mucosa for an unusually long period.

Toxicity and Sensitization Studies

The toxicity of the quaternary ammonium compounds in Tetronyl has been thoroughly studied by Shelanski.⁹ Acute oral toxicity studies indicate an LD₅₀ of 730 mg. per kilogram for rats, and 316 mg. per kilogram for guinea pigs. Dogs fed a 1:5,000 dilution as their drinking water daily for six months showed no disease of stomach, intestines, spleen, liver, kidney, heart, lungs, pancreas, or adrenals. In a two-year study on white rats with dosage levels as high as 25 mg. per kilogram daily, there was no significant deviation from control animals in weight gain, fertility, or mortality rate; blood and urine analyses showed no abnormality.

Sodium carboxymethylcellulose, the Tetronyl vehicle, has an extremely low toxicity. The LD₅₀ for white rats is 27 Gm. per kilogram and for guinea pigs, 16 Gm. per kilogram.⁸ A one-year study on guinea pigs and a 25-month

study on white rats revealed no gross or microscopic abnormality and no effect on urine, blood, or fertility when doses up to 1 Gm. per kilogram of body weight were given daily.

In contrast to almost all other compounds now used as trichomonacides, neither the active agent nor the vehicle of Tetranyl, even in concentrations far higher than those used clinically, shows evidence of being a primary irritant or a sensitizer when applied to the human skin.^{8, 9} There is no evidence of toxicity or sensitization when either substance is applied to the vaginal mucosa.

Method of Study

Subjects for this study of Tetranyl were drawn from the gynecological and obstetrical clinics of the Hospital of the University of Maryland. As a preliminary step, 985 women were surveyed for the incidence of *T. vaginalis* vaginitis. The results of this survey agreed in general with many that have been previously published. It will be noted that the clinic population in this hospital is predominantly Negro, and that the incidence of infestation in Negro women is almost three times as high as that in white women.

Patients were selected for treatment on the basis of two consecutive positive laboratory reports. As is usual with clinic patients, there was considerable difficulty in obtaining subjects cooperative enough to report regularly for treatment. Out of 149 started on this regime, 100 patients completed the treatment, at least to the extent of returning for a fourth check-up. This group, which is reported here, included 8 white and 92 Negro patients. All of the white patients were married; 63 of the Negroes were married, 29 were single.

Symptomatology, Physical Findings, and Diagnosis of *T. Vaginalis* Vaginitis

Classically, the symptoms produced by infestation with *Trichomonas vaginalis* are: leucorrhea; itching and burning, with chafing of the vagina and vulva. Less frequently there may be a sensation of heaviness in the pelvis and/or urgency or frequency of urination.

Incipient cases may be asymptomatic or exhibit symptoms of hyperemia of the portio vaginalis, with a nonmucoid discharge that is usually frothy, yellowish, or greenish-yellow in color, and may be slightly blood tinged. The discharge is so characteristic that a macroscopic diagnosis can usually, *but should not*, be made.

In patients with long-standing infestation, symptoms are more severe, the most prominent of which is intense itching, with profuse discharge. Associated extensive involvement of the labia majora and minora, with redness, sensitivity, and succulence, often make walking quite painful.

Laboratory diagnosis is greatly simplified by realization of the morphological and physiological individuality of the different organisms. It is no longer necessary to identify the species of trichomonad, since it is established that only *Trichomonas vaginalis* can live in specimens of vaginal discharge, urethral discharge, the first portion of a urine specimen, or the material expressed from Bartholin's or Skene's glands.^{1 (b)} Specimens for microscopic examination may be a drop from the speculum, or a smear taken from high up in the vagina, mixed with a drop of physiological saline solution or water.^{10, 11} Speculum must be dry and smear taken before digital examination. The typical picture of *Trichomonas vaginalis* shows a large number of pus cells, debris, few or no epithelial cells, and numbers of motile trichomonads about the size of a pus cell, in every field. The organism is transparent, but can be easily recognized by its constant, characteristic motion.¹⁰ Since *Trichomonas vaginalis* is the only flagellated protozoan found in the vaginal tract, it is unnecessary to use a dye or to make fixed, stained preparations.

Accompanying Disease

During examination, it is important to search for accompanying disease for two reasons: (1) *Trichomonas vaginalis* vaginitis may mask a condition of more serious import; (2) it is frequently useless to attempt to combat *Trichomonas vaginalis* vaginitis in the presence of other conditions such as cervical lesions, which favor its persistence.

Smears for gonorrhea should be taken simultaneously with the specimens to be examined for *Trichomonas vaginalis*; the clinical history and findings in the two diseases are often similar.¹⁰ In older age groups, the possibility of malignant disease must be considered¹¹ for the discharge from the vaginitis may mask a malignant focus in the upper genital tract. This was well illustrated in a recent patient who had a malodorous discharge with a persistent *Trichomonas vaginalis* vaginitis. Further examination showed that the leucorrhea arose from a fundal carcinoma which had been overlooked because the patient did not show the usual malignancy symptom of bleeding.

Effective treatment in all cases requires the correction of any coexisting disease in either the urinary or genital tract, as well as eradication of the trichomonad infection.

TABLE I. INCIDENCE OF INFESTATION

	NEGRO	WHITE
Number	771	214
Number of positive smears	258	26
Per cent of infestation	33.4	12.1

Reinfection

Autogenous reinfection, from foci located in Skene's glands, Bartholin's glands, and the cervix, is so common that effort should be made to eradicate the parasites from these extravaginal sites.

Trichomonads found in any part of the urinary tract may serve as a source of reinfection of the vagina. Cystoscopy may show diffuse inflammation of the bladder, the trigone appearing congested and reddened. In some cases urethral changes include a roughened, gray appearance of the internal orifice, which may bleed easily, and a mucous membrane covered with red patches and gray areas.^{1 (a)}

It is recommended that, whenever possible, the husbands of patients be examined for *Trichomonas vaginalis* infestation of the urethra, prepuce, and prostate. Eradication of the parasite in both sexual partners is the ideal, in order to guard against reinfection.

Therapy

In this series of clinic cases, therapy consisted of one physician-administered treatment weekly with Tetronyl powder and two daily patient-administered treatments with Tetronyl jelly, for a period of up to four weeks. If a negative laboratory report was not obtained by that time, the treatment was considered a failure. Simultaneously with *Trichomonas vaginalis* therapy, the patient was treated for any condition, such as the presence of cervical lesions, which might be considered a factor tending to favor the persistence of vaginitis.

Techniques for both office and home use of Tetronyl are extremely simple.

Office Treatment.—Tetronyl powder was supplied in individual-treatment flexible tubes which, when pinched, puff out a cloud of powder. To deposit the powder, a suitable dry bivalve speculum was introduced into the vagina; the tube was then pointed into the opening and squeezed until all the powder had been puffed out (Fig. 2). Care was taken not to let the end of the tube

come into contact with the mucous membrane, since sodium carboxymethylcellulose is extremely hygroscopic and cakes if it becomes damp. The vagina was not washed prior to treatment; soaps or other detergents leave a residue that may inactivate Tetreryl.

The powder becomes jellied immediately on contact with the moist vaginal mucosa and penetrates into every crevice and fold, where it may be observed clinging tenaciously. The active agent is leached slowly, in therapeutic concentrations, from the colloidal mass, to act against all organisms—bacteria, fungi, and protozoa. The entire clinic treatment usually took only five minutes.

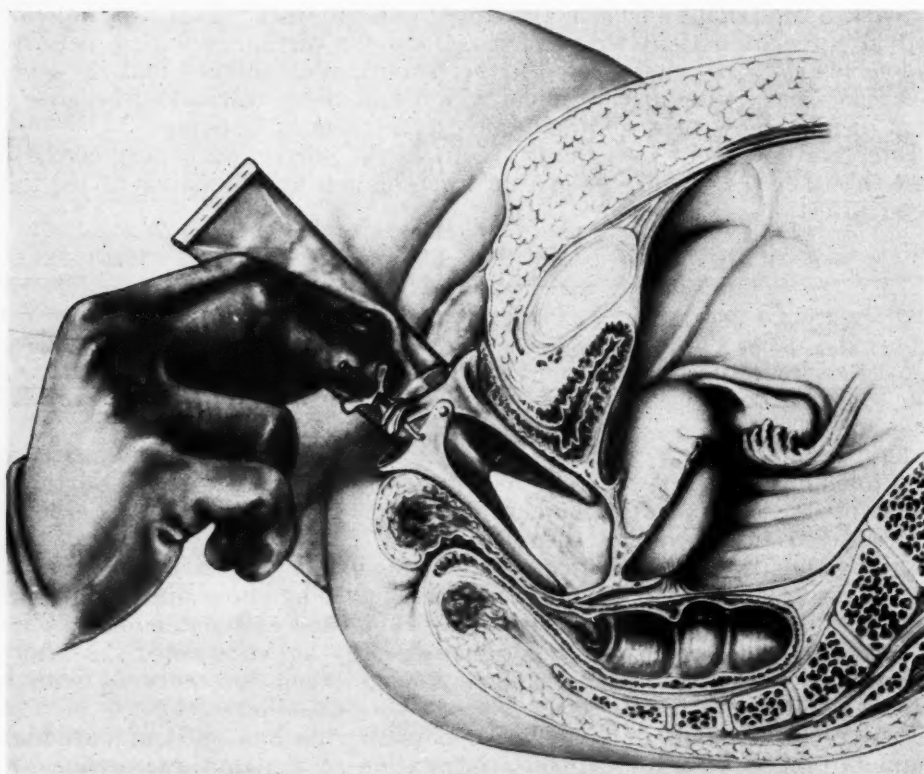


Fig. 2.—Simple office treatment of trichomonad infestation. Powder is puffed, without "ballooning" insufflation, from a single-dose flexible tube.

Home Treatment.—For home treatment, the patient was instructed to use two applicatorfuls of Tetreryl jelly a day. Because of mucosal sensitivity, flare-ups of the parasitism may be expected at or near the menstrual period. In addition, menstrual discharge provides an excellent medium for trichomonad development. Therefore, treatment should NOT be interrupted during the menstrual period.

Statistical Report of Cases

Treatment was successful in 94 of the 100 patients, the majority showing a negative laboratory report within one week:

Negative within 1 week	73
Negative within 2 weeks	90
Negative within 3 weeks	92
Negative within 4 weeks	94
Failures	5
Recurrence at third visit	1

Comment

There are probably few conditions for which more different medications have been tried than *Trichomonas vaginalis* vaginitis. Trussel, in his recent book,^{1 (a)} lists 172 preparations, but only about one-half dozen of these are now commonly used. There are definite drawbacks to the use of even those preparations which are most popular today. Most of these are arsenicals, picrates, and iodine-containing compounds, all of which may, and have, in certain instances, produced distressing drug reactions. Antibiotics and sulfonamides have proved of little value.^{1 (c)}

Some of the current preparations may also be criticized on the basis of their form: suppositories, tablets, capsules, solutions, and tampons give either inefficient distribution or a too-fleeting effect. Jellies have the advantage of mixing readily with the vaginal discharge and clinging to the mucosa for many hours if they are properly applied. This is the most satisfactory form for self-medication between office visits.

For office use, powders give good distribution and last long enough to be effective. However, those requiring air-pressure insufflation must be considered potentially dangerous. Six deaths have been reported as a result of air embolism following ballooning of the vagina. Such accidents may be avoided if the physician uses an open bivalve speculum and insufflates the powder directly on the mucosa. Because of its rapid, complete self-dispersion, Tetronyl powder does not require air-pressure insufflation in order to penetrate the vaginal rugae.

Although reports of 94 per cent successful treatment of *Trichomonas vaginalis* vaginitis are not unknown, we believe that the high percentage of cures obtained with Tetronyl within one week is unusual. For clinic work, where it is so difficult to get patients to return for regular treatment, a therapeutic regime that proved 73 per cent successful in only one week's time is of no particular significance.

In our hands, Tetronyl has proved rapidly effective as a trichomonacide. We have found it superior, in many respects, to products previously used in the treatment of *Trichomonas vaginalis* vaginitis. Its wide therapeutic activity, self-spreading action, prolonged retention, and lack of toxicity or sensitizing power are especially advantageous. In addition, Tetronyl is simple and convenient to use; is esthetically pleasing to the patient because it is an efficient deodorizer, will not stain clothing, and does not require the wearing of pads or tampons.

Summary

1. A new technique for the treatment of *Trichomonas vaginalis* vaginitis is reported. This technique requires only a speculum, and eliminates the need for "ballooning" insufflation, as well as for preparatory washing and drying of the irritated vagina.

2. This technique is made possible by the use of Tetronyl, a new surface-active trichomonacide that is self-spreading. In powder form, it is applied simply by puffing from a disposable single-treatment container. For self-medication between office visits, it is supplied as a jelly.

3. Tetronyl treatment of *Trichomonas vaginalis* vaginitis was successful in 94 of 100 clinic patients. Seventy-three of these were reported to be negative on examination within one week and 90 within two weeks.

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CESAREAN SECTION. A TEN-YEAR SURVEY IN A SMALLER HOSPITAL*

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THE trend toward liberalization of the indications for cesarean section, commensurate with the comparative safety of its performance, has been generally acknowledged. The incidence is increasing. There is some variation in comparable statistics depending upon factors which D'Esopo¹ has enumerated as: ratio of ward to private patients; the number of applicants from which the patients are chosen; race; the standing of a given hospital in a community; the policy and organization of the obstetrical staff. Table I illustrates this variation.

TABLE I. CESAREAN SECTION RATES¹

	PER CENT
New Haven Hospital	5.9
Margaret Hague	2.6
Chicago Lying-in	5.5
New York-Cornell	2.1
Boston City Hospital	4.2
Kansas City	7.1
Johns Hopkins Hospital	5.5
Cleveland Maternity	6.1
Philadelphia Lying-in	5.8
Sloane Hospital	5.8
Average	4.9

Coincident with the trend there has occurred a change in the attitude toward the cesarean section rate. Ten years ago a rate of 4 per cent was considered high and anything beyond that required explaining. Today the reverse is true and there is a tendency to question whether a service with a low cesarean incidence is practicing the best obstetrics within the limits of its own material.

We believe that current cesarean section rates are unnecessarily high and unless the trend is reversed the hazard of pregnancies subsequent to this type of delivery will more than offset the increased safety of the operation. The present study was undertaken to test the validity of this thesis.

We have held that a successful delivery through the natural passages is an achievement superior to delivery by an abdominal operation. Granting that the increased safety of the operation now permits some liberalization of the indications, it seems also that the factors which make the operation safer (i.e., better technique, better anesthesia, antibiotics, blood transfusions, etc.) will permit an increased period of delay before operation and in some cases avoid it entirely. This will in some measure prevent a too rapid rise in incidence. We still feel

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that an inordinately high cesarean section rate is indicative of a lack of obstetric art or of a disregard of the patient's future obstetric well-being. The subsequent rupture of a cesarean scar may not be included in the operator's statistics but should certainly be his responsibility.

Material

The material presented includes a survey of cesarean sections performed at the Pittsburgh Hospital from Jan. 1, 1940, to Dec. 31, 1949 (Table II). The institution is a general hospital of about two hundred twenty-five beds. It is strictly departmentalized. A very minor part of the normal obstetrics is performed by a small courtesy staff which is subject to staff consultation in all cases which do not deliver as spontaneous vertex presentations after average labors.

TABLE II. CESAREAN SECTION INCIDENCE

YEAR	DELIVERIES	CESAREAN	INCIDENCE (%)
1940	731	7	0.96
1941	797	7	0.88
1942	1,023	9	0.88
1943	946	6	0.63
1944	914	13	1.42
1945	940	7	0.74
1946	1,179	12	1.02
1947	1,423	18	1.26
1948	1,249	18	1.44
1949	1,297	21	1.70
10 years	10,499	118	1.09

It is noted that there has been a gradually increasing incidence of cesarean sections, especially over the last four-year period. The figure of 1.7 per cent for 1949 is still lower than any published figures that we have seen.

Table III reveals that of 118 operations the patient was over 30 years of age in 69. Our mothers fall into the usual age groupings of maternity patients, preponderantly between 19 and the early thirties. The above figures reveal not only the higher incidence of abdominal delivery in the older primiparas, but also our reluctance to section a young woman who must face a long period of potential childbearing with a scar in her uterus.

TABLE III. AGE INCIDENCE (YEARS)

	18-20	20-29	30-39	OVER 40
1940		4	3	
1941		3	3	1
1942	1	3	4	1
1943	1	1	4	
1944		5	7	1
1945		1	4	2
1946		6	2	4
1947		9	9	
1948		6	10	2
1949		9	9	3
	2	47	55	14

The table of gravidity (Table IV) shows just what might be expected: most operations are performed on primiparas, the great majority are before the fourth pregnancy, but grand multiparity is not insurance against an accident of pregnancy which may best be treated by cesarean section.

TABLE IV. GRAVIDITY

	i	ii	iii	iv	v	vi	vii	viii	ix	xii
1940	3	2	1	1						
1941	3	2	2							
1942	4	1	3	1						
1943	1	1	3	1						
1944	4	5			2	1	1			
1945	3	1	2		1					
1946	4	2	3	1			1		1	
1947	6	5	3	2	1			1		
1948	4	7	1	2		2		1		1
1949	6	5	6	1	2	1				
	38	31	24	9	6	4	2	2	1	1

The indications total 122, in 118 patients, because several patients had to be included in more than one category (Table V).

TABLE V. INDICATIONS

<i>Bleeding</i>	
Placenta previa	31
Placenta previa and previous section	1
Placenta previa and leiomyoma	1
Abruptio placentae	16
Abruptio placentae and previous section	1
	50
<i>Contracted Pelvis</i>	
Plus breech presentation	1
Plus pre-eclampsia	1
Plus one previous cesarean	18
Plus two previous cesareans	6
Plus three previous cesareans	2
Plus four previous cesareans	1
Plus five previous cesareans	1
	43
<i>Old Primiparity</i>	
Aged 40 and 44—with nonengagement	2
Aged 38 and 40—with floating breech	2
Aged 40 —with hypertension and contracted pelvis	1
Aged 41 —with pre-eclampsia and fibroids	1
with degenerating leiomyomata	2
	8
<i>Toxemias</i>	
Progressive pre-eclampsia	2
Progressive pre-eclampsia and leiomyoma	1
Progressive hypertension	3
Chronic nephritis, hypertension, previous section	1
	7
<i>Miscellaneous</i>	
Perforation in previous curettage and transverse presentation	1
Cervical dystocia and fetal distress	1
Primary inertia. Previous stillbirth	1
Primary inertia. Prolapsed cord	1
Diabetes mellitus	3
Heart disease	1
Multiple sclerosis. Leiomyoma	1
Previous cesarean and	
Ruptured uterus	1
Incomplete rupture of uterus	1
Febrile convalescence	1
Febrile convalescence and twins	1
Primary inertia and twins	1
	14

Fifty of 118 operations were performed because of bleeding from placenta previa or abruptio placentae. This group accounts for a considerable percentage of the increased incidence of cesarean section. We discontinued the use of hydrostatic bags in placenta previa some time before the period encompassed in this study. The ease with which infections are prevented and controlled by chemotherapy and antibiotics has led us to consider the advisability of an occasional use of the bag, but we have been deterred by the increased attendant fetal risk. Many cases of low implantation are efficiently and safely handled by simple vaginal procedures such as rupture of the membranes. Cases of premature separation are delivered abdominally or vaginally depending upon local and general conditions in the mother and the condition and maturity of the baby. We use the blood bank generously.

Contracted pelvis was the indication in forty-three patients. Twenty-eight of these patients had had previous section. One each had had four and five previous operations, respectively. Might not the increased safety of the operation suggest a reappraisal of the practice of arbitrarily restricting the individual's family to one or two children?

We do not routinely repeat cesarean section unless the original operation was done for an absolute indication. Our procedure closely parallels that outlined by Herbert E. Schmitz² of Chicago and Daniel H. Hindman³ of Boston Lying-in Hospital.

We have discarded the classical operation in favor of the low segment double flap procedure. Formerly we used the classical operation in our elective operations but have been impressed by figures which indicate there is two and one-half times more likelihood of rupture after the older operation. We have gradually discarded the low longitudinal incision of Beck in favor of the transverse semilunar one suggested by Phaneuf. It is easier to expose the lower segment, especially where it has not been thinned out by a test of labor, the upper peritoneal flap is less likely to tear, and the incision is lower in the pelvis. Occasionally in placenta previas where there are unusually large sinuses laterally, we still employ the longitudinal incision in the uterus.

The four cesarean hysterectomies were done in older patients with large fibroids. Two of these showed advanced degeneration. A third patient had, in addition, advanced multiple sclerosis, and the fourth had decompensated rheumatic heart disease.

TABLE VI. TYPE OF OPERATION

YEAR	CLASSICAL		CERVICAL B		CERVICAL P		PORRO	
	NO.	%	NO.	%	NO.	%	NO.	%
1940	5	71	2	29				
1941	5	71	1	14.5	1	14.5		
1942	5	55.5	1	11	3	33.5		
1943	4	67			2	33		
1944	9	69			4	31		
1945	4	58			3	42		
1946	7	59			3	24	2	17
1947	12	67			6	33		
1948	4	22			12	67	2	11
1949			1	4.8	20	95.2		
10 years	55		5		54		4	

Tables VII and VIII illustrate the type of operation performed in relation to labor and the condition of the membranes. We have not used the classical operation in labor since 1940 except in one case, in 1948, where the scar of a previous elective operation had ruptured. In ten years the classical operation

has been done three times when the membranes had ruptured. The last time was in 1943. In 1941 the procedure performed on a patient whose membranes had ruptured twenty-four hours previously gave us one of our most severe morbidities.

TABLE VII. TYPE OPERATION IN RELATION TO LABOR

YEAR	NOT IN LABOR		1-12 HOURS		OVER 12 HOURS	
	CLASS.	CERV.	CLASS.	CERV.	CLASS.	CERV.
1940	4	2	1			
1941	5	1		1		
1942	5	1		3		
1943	4	1				1
1944	9	2		2		
1945	4			1		2
1946	7	2		1		
1947	12	3		1		2
1948	3	8	1 rupture	3		1
1949		17		2		2
	53	37	2	14		8
			4 Porro's			

TABLE VIII. TYPE OF OPERATION IN RELATION TO MEMBRANES

YEAR	INTACT		1-12 HOURS		13-24 HOURS	
	CLASS.	CERV.	CLASS.	CERV.	CLASS.	CERV.
1940	4	1	1	1		
1941	4			1	1	1
1942	5	3		1		
1943	3		1			2
1944	9	3				1
1945	4	2		1		
1946	7	2				1
1947	12	4		1		1
1948	3	10		1		2
1949		19		1		1
	51	44	2	7	1	9
			4 Porro's			

The choice of anesthesia had gradually changed from nitrous oxide ether in the early years to spinal or saddle block with heavy Nupercaine. Nitrous oxide oxygen induction with Pentothal Sodium beginning with delivery is being found very useful. Our patients are now in better condition postoperatively. They have no nausea or vomiting, little abdominal distention, and the baby is not narcotized.

TABLE IX. ANESTHESIA

	GAS ETHER	PENT. SOD. O ₂	CAUDAL	LOCAL GAS	PENT. SOD. GAS	SPINAL	LOCAL PENT. SOD.	SADDLE BLOCK
1940	7							
1941	6	1						
1942	9							
1943	6							
1944	9	1	1	1	1			
1945	4				2	1		
1946			2		9	1		
1947	2				9		4	3
1948					14		1	3
1949					6	6	1	8
	43	2	3	1	41	8	6	14

There was no maternal mortality in this series. The morbidity (a temperature of 100.4° F. occurring on 2 days of the postpartum period exclusive of the first 24 hours) is shown in Table X. Six seriously morbid cases are described, in the right column. The decline in morbidity since the advent of the antibiotics is especially noticeable. We now give penicillin routinely pre- and postoperatively, with sulfonamides or streptomycin as indicated. There has been a slow but steady decrease in the number of postoperative hospital days. We feel that early ambulation has contributed to this.

TABLE X. MORBIDITY

YEAR	OPER.	MORBID		SLIGHT FEVER 1-3 DAYS	POST- OPER. DAYS	EXCEPT BELOW
		NO.	%			
1940	7	5	71	5	14 plus	
1941	7	6	85	5	14 plus	Phlebitis. Class. oper. for pl. previa. Not in labor. Membr. rupt. 24 hrs. In hosp. 27 days.
1942	9	5	56	5	14½	
1943	6	2	33	1	13 plus	Disruption of wound. Pneumonia. Cervical sect. for disproportion—2nd sect. Labor 22 hrs. Memb. rupt. 3 hrs. In hosp. 30 days.
1944	13	5	38	4	14 minus	Phlebitis. Class. oper. for pl. abruptio. Not in labor. Membr. intact. In hosp. 26 days.
1945	7	2	29	2	12 plus	
1946	12	4	33	2	11 4/5	Pre-oper. cold. Disruption of wound. Class sect. for pl. abruptio. No labor. Membr. intact. In hosp. 20 days. Atelectasis. Class sect. plus myomectomy for pl. abruptio. No labor. Membr. intact. In hosp. 19 days.
1947	18	2	11	1	11 plus	Pre-oper. bronchitis. Cerv. sect. for pl. abruptio. Not in labor. Membr. intact. In hosp. 11 days.
1948	18	4	22	4	10½	
1949	21	4	18	4	10	
	118	39	33	33		

Table XI shows the fetal mortality in this series. The mortality from prematurity in placenta previa is being improved by a policy of expectancy with the patient under observation in the hospital until symptoms demand intervention or the baby is large enough to be reasonably secure outside the uterus. In abruptio placentae and nephritis with placental infarction the fetal oxygen supply is interfered with. The fetal heart sounds may be good but the period of relative anoxia may have compromised the fetus to the point where it is stillborn or perishes shortly after birth. Table XI demonstrates this point and it is a good one to remember. These babies also do better without general anesthesia.

In any cesarean section study, particularly where the incidence of operation is low, it must be correlated with a study of fetal mortality. Dr. William Gibson⁶ of our staff has made a thorough investigation of all aspects of our fetal loss and we are submitting his study so that it may be correlated with our own. The figures are from 1947 to 1949, inclusive.

TABLE XI. FETAL MORTALITY—16 (13.5%)

BIRTH WEIGHT GM.	ANESTHESIA	DIED
<i>Placenta Previa</i>		
2,085	Gas-Ether	1 day
1,815	Gas-Ether	2 days
1,935	Gas-Ether	1 day
1,720	Gas-Ether	1 day
1,360	Caudal	2 days
2,270	Saddle	5 days (Kernicterus)
2,720	Saddle	1 day
Total Previas	33	Died 7 (21.2%)
<i>Abruptio Placentae</i>		
Term	Spinal	Stillborn
1,815	Spinal	Stillborn
1,360	Gas-Spinal	10 minutes
1,360	Gas-Spinal	3 days
?	Gas-Ether	15 minutes
Total Abruptio	17	Died 5 (29.2%)
<i>Miscellaneous</i>		
<i>Essential Hypertension—Previous Section</i>		
1,589	Caudal	Died 3 days
<i>Hypertension 240/140—Neuroretinitis</i>		
1,400	Local-Gas	Died 2 days
<i>Nephritis—Hypertension—Leiomyoma—Pr. Sect.</i>		
1,362	Caudal	Stillborn
<i>Cephalo-pelvic Disproportion (Labor Test)</i>		
4,540	Spinal	Died 24 hours (Aspiration pneumonia)

It is difficult to compare figures on fetal loss. There are no standards for comparison. Viability may be based on birth weight or chronologic age. Still-birth rates may be based on postviable stillborns or pre- and postviable. Fetal loss may be estimated from the number of deliveries or the number of live births. We submit Table XII with these differences in mind. The figures from Pennsylvania and from the U. S. Registration Area include the loss of babies over 20 weeks' gestation who have died in institutions in these areas in comparison with the number of live births in the same areas.

TABLE XII

	DELIVERIES	LIVE BIRTHS	STILLBIRTH RATE	FETAL LOSS
Chicago Lying-in 1941-1946		17,436	19	2.5% (over 28 weeks)
Pittsburgh Hospital 1947-1949		3,875	9.5	2.05% (over 28 weeks)
Long Island Coll. 1940-1944	7,580			2.63%
New York & Sloane 1935-1940	28,823			3.52%
Margaret Hague 1948		8,758	16.5	3.57% (Inc. previable) (stillbirths)
State of Pennsylvania 1947		248,513	20.2	4.03% (Institutions only)
U. S. Registration Area		3,699,940	23.7	4.46% (Institutions only)

In this study the two fetal figures which are important are the intra-partum stillbirths and the neonatal deaths. Table XIII is an analysis of our fetal loss. The 2 term intrapartum stillborns who were listed as due to obstet-

Case 4 should have had a hysterectomy and more adequate blood replacement.

Case 9 would have been prevented by cesarean section or by postpartum hysterectomy when the placenta did not separate spontaneously.

TABLE XV. MATERNAL MORTALITY FOR ALL OBSTETRIC PATIENTS

YEAR	PATIENTS	DEATHS
1940	731	0
1941	797	0
1942	1,023	3
1943	946	0
1944	914	2
1945	940	1
1946	1,179	2
1947	1,423	0
1948	1,249	1
1949	1,297	3
10 Years	10,499	12—0.11%

TABLE XVI. MATERNAL DEATHS, 1940-1949

1942—	1. Rheumatic heart. Cardiac death at 20 weeks.
	2. Forty-year-old eclamptic—intracranial hemorrhage
	3. Postpartum eclampsia—admitted after twin delivery at home
1944—	4. Postpartum hemorrhage—spont. delivery—uterine atony
	5. Aspiration of vomitus during gas-ether anesthesia
1945—	6. Fulminating eclampsia
1946—	7. Aspiration of vomitus during gas-ether anesthesia
	8. Suicide—psychiatric—jumped from sixth floor window
1948—	9. Unrecognized perforation of old myomectomy scar during manual removal of placenta
1949—	10. Eclampsia—transient patient. Moribund on admission
	11. Fulminating eclampsia. Intracranial hemorrhage. Rupture of posterior cerebellar artery
	12. Spontaneous subarachnoid hemorrhage 13 hours post partum

Summary

1. A ten-year survey of cesarean sections in a small general hospital is presented.
2. The incidence in 10,499 deliveries was 118, or 1.09 per cent.
3. The mortality in cesarean section was: maternal, none; fetal, 13.5 per cent.
4. The total ten-year mortality was: uncorrected maternal, 0.11 per cent; total fetal loss, 4.39 per cent; corrected fetal loss, 2.05 per cent.

Conclusions

The current incidence of cesarean section is generally too high, and unless the trend is reversed many mothers will be exposed to an unjustifiable hazard in subsequent pregnancies.

Good maternal and fetal results can be attained with a comparatively low incidence of abdominal delivery.

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THE PRESENT-DAY SAFETY OF CESAREAN SECTION

A Review of 1,192 Cases With No Maternal Mortality

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AT PRESENT, it is agreed that cesarean section in competent hands is a much safer operation than in previous years. This opinion is documented by many writers who are reporting increasingly larger series of cases with little or no maternal mortality.^{1, 3, 4, 5}

In 1933, Seeley¹ reported a series of 134 consecutive sections performed with no maternal deaths, truly a remarkable achievement for that time. Eighty-three of these patients were not in labor when operated upon. In 1934, Stander² stated that cesarean section carries a maternal mortality of close to 10 per cent, and some series reported a mortality up to 16 per cent. DeNormandie,³ in 1938, summarizing the 2,232 sections in the state of Massachusetts, found a gratifyingly low maternal mortality of 2.7 per cent. Mack and Siddall,⁴ reporting the section rate in Detroit for different decades, show a maternal mortality of 13 per cent in 1925; 4.4 per cent in 1930; and only 0.8 per cent in 1945. Dieckmann⁵ recently reported that since July 1, 1942, he and his group have performed 860 consecutive sections with no maternal deaths.

These data suggest that obstetricians today have justification for undertaking sections with a greater sense of security and with a resultant broadening of indications for the operation.

Material

Our series at the Millard Fillmore Hospital, covering a period from Nov. 16, 1945, to Aug. 17, 1949, includes 14,591 deliveries, of which 1,192 (8.16 per cent) were cesarean sections. Of these 503 (42.2 per cent) were low cervical in type, 606 (50.8 per cent) were classical, 65 (5.5 per cent) were Porro, and 18 (1.5 per cent) were extraperitoneal.

The vast majority of the classical sections were done by two separate operators who believe that this is the procedure of choice. All of the extraperitoneal sections were done by two other operators using the Latzko technique. With these facts in mind, it should be noted that the greater number of operators in this clinic prefer the low-segment type of operation.

A total of 32 operators, including residents, performed this series. Nine hundred seventy-two operations were done by obstetrical specialists, 120 by nonspecialists.

Two hundred ninety-three cases (24.6 per cent) were classified as emergency in nature and were composed largely of placenta previa with bleeding, severe abruptio placentae, long unsuccessful tests of labor, and marked fetal distress. Eight hundred ninety-nine cases (75.4 per cent) were classified as elective. This accords closely with Irving's series in 1945⁶ in which were reported 27.9 per cent emergency and 72.1 per cent elective.

In this series 26.7 per cent of the patients were sterilized. Sterilization rates in other cities and hospitals range from 24.4 per cent up to 46.5 per cent.^{6, 7, 8}

This series includes 65 cesarean hysterectomies, of which 27 were done for coexistent fibroids, 25 for sterilization, 4 for uncontrollable hemorrhage, and 9 for miscellaneous indications. Some of these cases deserve special attention. Of three cases of ruptured uterus, two were spontaneous during the last trimester of pregnancy, through old classical-cesarean scars. One patient was in the seventh month of gestation, the other in the eighth month, and neither had experienced any labor during this pregnancy. Both were delivered of stillborn infants. In one case of an ovarian tumor as an indication for Porro section, it should be pointed out that the tumor was intimately adherent to the uterus and could not be completely removed without removal of both tumor and uterus. Hysterectomy was performed in a case of bowel obstruction to allow adequate exposure for the bowel surgery.

In 71 per cent of the cases general inhalation anesthesia was used and in the remainder spinal anesthesia.

The indications for section can be divided into sections before viability (under 1,500 grams) and those after viability. Nineteen patients were sectioned before viability. The indications are given in Table I. The indications for sections after viability are listed in Table II.

TABLE I. INDICATIONS FOR CESAREAN SECTION BEFORE VIABILITY (UNDER 1,500 GRAMS)

Placenta previa	4 or 0.34%
Abruptio placentae	2 or 0.17%
Toxemia	8 or 0.67%
Medical-surgical complication	2 or 0.17%
Miscellaneous	3 or 0.25%

TABLE II. INDICATIONS FOR CESAREAN SECTION AFTER VIABILITY (OVER 1,500 GRAMS)

Cephalopelvic disproportion	497 or 41.59%
Previous cesarean section	318 or 26.68%
Medical-surgical complication	62 or 5.20%
Soft-tissue dystocia	59 or 4.95%
Abruptio placentae	55 or 4.65%
Placenta previa	46 or 3.86%
Toxemia	46 or 3.86%
Elderly primipara	33 or 2.77%
Fetal distress (cause not known before operation)	25 or 2.10%
Malposition of fetus	20 or 1.67%
Possible erythroblastosis of fetus (rising titer)	12 or 1.01%

There were five sets of twins (1.01 per cent) and one set of triplets delivered by cesarean section.

Five hundred seventy patients (47.8 per cent) received transfusions of whole blood, of whom 427 received only 500 c.c. It is routine to have 500 c.c. of blood typed and cross matched for the patient in the surgery at the time of each section, available for immediate use. With certain operators it is customary to start blood at the beginning of the operation, anticipating blood loss, for prophylaxis against shock, and as a good supportive measure for the patient. Other operators prefer to use blood only when they feel it is indicated in a particular case, as for excessive blood loss, but do not use it routinely. The patients treated for shock totaled 34 (2.9 per cent). Most of them were in moderate or mild degree of shock and responded readily to treatment. A small

number of patients developed profound shock. Although prompt transfusion was instituted in all such cases, a rare case presented such a grave and critical picture that we cannot deny that the element of good fortune as well as skill played a part in avoiding a mortality.

Three hundred forty patients (28.5 per cent) were packed before closure of the uterus. Three hundred thirteen of these were elective packing and 27 were packed because of excessive bleeding. All the elective packing was done by two surgeons who routinely employ this procedure in their sections, using an iodoform pack. This pack is usually removed in twenty-four hours through the birth canal.

In determining the maternal morbidity in this series we followed the *International Standard* definition. There were 301 cases (25.2 per cent) of morbidity. In over half of the cases the duration of morbidity was only two days, and in most cases was due to so-called reaction temperature immediately following operation. The incidence of morbidity with the different types of section is listed in Table III. *It is interesting to note that the classical section showed a lower incidence of morbidity than the other types of sections.* A possible explanation may be in the fact that more of the classical sections were of the elective type than were the low-cervical procedures.

TABLE III. MORBIDITY ACCORDING TO TYPE OF SECTION

TYPE	NO. CASES MORBID	PERCENTAGE OF TOTAL
		NO. OF EACH TYPE SECTION
Classical	133	21.9%
Longitudinal low cervical	107	27.4%
Transverse low cervical	35	30.9%
Cesarean hysterectomy	19	29.2%
Extraperitoneal	7	38.9%

In this series it was not the universal custom to give penicillin prophylactically. However, 316 (26.5 per cent) patients in this series did receive this drug. One hundred fifty-nine (52.8 per cent) of the morbid patients received penicillin, which indicates that the picture was not alarming in nearly half of these morbid patients. There were 3 cases of pneumonia (apparently of the aspiration type) in the entire series and these showed the greatest number of days of morbidity.

Appendectomy was performed in 127 cases of section (10.65 per cent). In all these cases the appendectomy was an elective procedure, and the appendix was grossly normal. One hundred of these patients in whom appendectomy was performed, had no morbidity; 13 were morbid two days; 9 were morbid three days; 4 for four days; and one for five days. Thus the total number of cases of morbidity following section and appendectomy was 27, or 21.6 per cent, which compares favorably with the over-all section morbidity of 25.2 per cent. This series at least would seem to indicate that removal of the appendix at time of section is a relatively safe procedure. However, it must be pointed out that the majority of sections in which appendectomy was performed were of the elective variety and the outlook was consequently more favorable.

In the entire series there were 63 fetal deaths (5.3 per cent), of which 49 fetuses were viable and 14 nonviable. The over-all corrected mortality was 2.3 per cent. This corrected figure excludes: erythroblastosis, congenital anomalies, maceration, prematurity (under 2,500 grams), and nonviability (under 1,500 grams). The causes of stillbirth and neonatal death are listed in Table IV.

In any large series of operative cases the unforeseen and nonpreventable deaths will always intrude. This event finally ended our series in August, 1949,

when a young woman eight months pregnant was admitted to the Millard Fillmore Hospital because of acute poliomyelitis. She was placed in a respirator and in twenty-four hours was approaching a moribund condition. Section was decided upon in the hope of giving respiratory relief and of saving the child. Under local infiltrative anesthesia the abdomen was opened and a child weighing 5 pounds, 4 ounces, was delivered in good condition. The mother improved appreciably and did well for three days, but then developed embarrassment from tracheobronchial secretions. An emergency tracheotomy was performed but did not give much relief. She expired on the fifth postoperative day. Autopsy revealed the tracheobronchial tree filled with thick, tenacious plugs of mucus. The uterus and abdominal area showed no abnormality beyond normal healing process. Microscopic sections of the spinal cord and brain confirmed the diagnosis of acute ascending cervical poliomyelitis. The baby did well, did not contract the disease, and was discharged in good condition. Aside from this death, for which correction may be made, there have been no further maternal deaths from cesarean section up to the present time.

TABLE IV. CAUSES OF STILLBIRTHS AND NEONATAL DEATHS

	VIABLE INFANTS	NONVIABLE INFANTS
<i>A. Stillbirths.—</i>		
Asphyxia	16	2
Toxemia	1	1
Macerated stillborn	2	1
Prematurity	1	0
	<u>20</u>	<u>4</u>
<i>B. Neonatal Deaths.—</i>		
Prematurity	7	8
Congenital defects	8	2
Atelectasis	10	0
Erythroblastosis	4	0
	<u>29</u>	<u>10</u>

Comment

It will be noted that our incidence of extraperitoneal sections is low. This low figure is due largely to the fact that in this clinic patients with borderline pelvises (and/or cephalopelvic disproportion) are not allowed active labor without progress beyond twenty-four hours, particularly when the membranes have ruptured. Thus, we usually do not have to operate upon infected patients. In those cases where infection is either obviously present, or highly probable, we do feel that extraperitoneal section is the procedure of choice.

As to the problem of vaginal delivery following cesarean section, our experience in the past has led us to adhere largely to the dictum of "Once a section, always a section." We feel that it has been proved by and large that repeat cesarean is safer for mother and child than risking vaginal delivery with the ever-present possibility of rupture through the previous cesarean scar with almost certain fetal death and maternal risk. Although there are many well-known factors which influence cesarean scars, particularly endometriosis, infection, morbidity, sutures tied too tight, over-liberal use of catgut, and inherent poor healing qualities in an individual patient, really nothing can be assured about an individual scar at term pregnancy without actual gross and microscopic examination. We feel that with the relative safety of cesarean section today, the conservative procedure is to repeat section rather than to risk vaginal delivery.

One of our indications for cesarean section after viability is listed as fetal distress. We are fully cognizant of the fact that there are many good authorities who do not recognize this as a valid indication. These authorities believe that subsequent pregnancy is usually possible, and vaginal delivery with possible or probable fetal death is to be preferred before cesarean section. However, in a considerable number of these patients, pregnancy does not occur again. We feel that an obstetrician in accepting a case undertakes an obligation to deliver the mother of a living child if at all possible without serious risk to the life of the mother. Another objection raised against our point of view is that family size in a primipara will be limited to no more than three or four children. In reality, today, the tendency is to have no more than three or four children in the family, and frequently but one or two, irrespective of the methods of delivery.

The question naturally arises as to how many cesarean sections an average patient can be permitted to have. In our clinic we have generally, with an occasional exception, adhered to the following policy: consider sterilization with the second section, perform it usually with the third, and almost invariably with the fourth.

It should be noted that 12 patients were sectioned because of possible erythroblastosis, evidenced by a rising titer in the last six weeks of pregnancy. Because they were not at term these patients were not well suited for induction. Immediately after delivery complete blood studies were done, and, if a diagnosis of erythroblastosis amenable to treatment was established, appropriate measures were undertaken. In the 12 cases, 8 babies showed definite erythroblastosis and 4 of these were subjected to exsanguination transfusion. One of the four died, as did one severely erythroblastotic baby not treated by exsanguination transfusion. Three babies showed a mild degree of erythroblastosis and recovered without exsanguination transfusion. Four patients who were sectioned because of possible erythroblastosis gave a history of previous erythroblastotic infants, and three showed a rising blocking antibody titer in the present pregnancy. In these four cases, however, the baby proved to be Rh negative with an essentially normal blood picture.

It would seem that we have saved some babies from almost certain erythroblastotic death by timely and appropriate intervention.

We believe that the following factors are responsible for the absence of maternal deaths in this series:

1. Consultation by qualified specialists is required on all cases in which labor has lasted over twenty-four hours and which exhibit any unusual complication. Therefore, the only neglected cases in this series were those which were brought in from the outside after many hours of labor and/or inept attempts at delivery.

2. The availability and liberal use of whole blood and antibiotics. A pint of Group 4-O RH-negative blood with Witebsky anti A and anti B substance added is available at all times, so that whole blood therapy can be instituted almost immediately when necessary, while further blood, if required, is being typed and cross matched.

3. The majority of the sections, 972 (81.5 per cent), were performed by obstetrical specialists.

4. The advent of the recovery room established in September, 1945, coincided with the marked drop in maternal mortality in sections, as shown by the statistics in Table V.

TABLE V. MATERNAL MORTALITY RATE IN CONSECUTIVE YEARS AT THE MILLARD FILLMORE HOSPITAL

YEAR	DELIVERIES	SECTIONS	PERCENTAGE OF SECTIONS	SECTION MATERNAL MOR- TALITY RATE (PER CENT)
1937	1,426	154	10.8	1.8
1938	1,725	139	8.0	2.5
1939	1,441	132	9.2	4.0
1940	1,866	119	6.3	4.3
1941	2,265	139	6.2	1.4
1942	3,067	193	6.3	1.0
1943	3,773	302	8.0	2.6
1944	3,095	256	8.2	1.1
1945	3,123	241	7.6	0.8
1946	3,578	308	8.1	0.0
1947	4,049	334	8.2	0.0
1948	3,948	313	7.9	0.0
1949	4,185	339	8.1	0.3*

*This figure is accounted for by the death from poliomyelitis and is therefore correctable to 0.0. The figures for 1949 in the above table include all deliveries and sections performed during the entire year, not just the period included in this report.

The recovery room is a specialized ward wherein every patient is placed immediately after delivery, either vaginal or abdominal. The patient remains there for a period of at least eight hours, during which time she is under the constant care of a specially trained nurse who notes and records the patient's blood pressure, pulse, condition of fundus, vaginal flow, and general condition every half hour. Any unusual alteration in a patient's condition is immediately reported to an obstetrical resident who has authority to institute any required emergency treatment without delay.

Conclusions

1. Cesarean section today is an increasingly safe procedure for both mother and baby.
2. Due to this increased safety the indications can be broadened in the interests of the infant as well as the mother.
3. Earlier intervention instead of hopeful procrastination will result in lowered maternal and fetal mortality.
4. The liberal use of blood and antibiotics will contribute significantly to a lowered maternal mortality.
5. In this Hospital, the use of the recovery room has lowered the maternal death rate from hemorrhage to the vanishing point. No deaths from hemorrhage connected with sections have occurred since the advent of the recovery room.

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826 WEST DELAVAN AVENUE

EXTRAPERITONEAL CESAREAN SECTION: A REVIEW OF SEVENTY-ONE CONSECUTIVE OPERATIONS*

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SEVENTY-ONE extraperitoneal cesareans have been performed by us between Nov. 15, 1941, and Jan. 21, 1950. The following is a report of these operations together with an account of the evolution of our operative technique and postoperative management during this experience. Since the beginning of this series of cases we have performed no cesarean hysterectomies or craniotomies on infected parturients.

Indications

The principal indications for abdominal delivery are analyzed in Table I. Sixty-two operations were performed with fetopelvic disproportion of some degree as the principal indication. Six secondary cesareans followed primary cesareans for disproportion; of the primary operations, 3 had been of the extraperitoneal type. Three cesareans for placenta previa were performed after hemorrhage had subsided; of these, one patient had had ruptured membranes for two days. Supplementary indications existed in many cases, to wit: uterine atony in 9, persistent occipitoposterior in 7, and pre-eclampsia in 5 cases. Of 57 primigravidas, one was 19 years of age, 36 were in the third decade, 19 in the fourth decade, and one was 42 years of age. Of 14 multigravidas, 7 were in the third and 7 were in the fourth decade of life.

TABLE I. PRINCIPAL INDICATIONS FOR ABDOMINAL DELIVERY IN SEVENTY-ONE CONSECUTIVE
EXTRAPERITONEAL CESAREAN SECTIONS*

Fetopelvic disproportion		62
Vertex presentation	52	
Breech presentation	8	
Transverse lie	2	
Previous cesarean section for disproportion		6
One previous extraperitoneal cesarean	3	
One previous transperitoneal cesarean	2	
Two previous transperitoneal cesareans	1	
Placenta previa (no bleeding at time of operation)		3
Complete	2	
Partial, membranes ruptured two days	1	
Total	71	71

*Supplementary indications existed in many cases, namely, uterine atony in 9, persistent occipitoposterior in 7, and pre-eclampsia in 5 cases.

The extraperitoneal route was indicated (Table II) in 49 operations by the criteria of Cosgrove and Norton,¹ namely, labor of twenty-four or more hours' duration, ruptured membranes in excess of twelve hours, clinical evidence of infection, or previous vaginal examination or attempts at delivery.

*Presented at a meeting of the Obstetrical Society of Boston, March 21, 1950.

The presence of a rectovaginal fistula just below the cervix was the indication for the extraperitoneal approach in one primigravida with borderline cephalopelvic disproportion and an unsatisfactory trial labor with intact membranes.

TABLE II. INDICATIONS FOR USE OF THE EXTRAPERITONEAL ROUTE IN SEVENTY-ONE CONSECUTIVE EXTRAPERITONEAL CESAREAN SECTIONS. FOURTEEN OPERATIONS WERE PERFORMED IN THE ABSENCE OF LABOR

The criteria of Cosgrove and Norton (J.A.M.A. 118: 201, 1942)		49
Labor of 24 or more hours' duration	26	
Membrane rupture of 12 or more hours' duration	36	
Previous vaginal examinations or attempts at delivery	14	
Clinical evidence of infection (fever 6, foul liquor amnii 3)	7	
High rectovaginal fistula (disproportion)		1
Elective use of extraperitoneal route		21
Fetopelvic disproportion	13	
Repeat cesarean sections	6	
Placenta previa (no bleeding at time of operation)	2	
Total		71

Twenty-one operations—13 for fetopelvic disproportion, 6 repeat cesareans, and 2 for placenta previa—were performed electively by the extraperitoneal route for teaching and demonstration purposes, to augment our own experience, or where a septic procedure preceded cesarean section in the only operating room of a small hospital.

Fourteen operations—5 secondary cesareans, 3 for placenta previa, and 6 for disproportion—were done in the absence of labor.

Operative Technique

In this series of operations we have employed the unilateral paravesical approach of Latzko² twice, the unilateral paravesical approach of Norton³ or Irwin⁴ twelve times, the supravesical approach of Waters⁵ fifteen times, and the bilateral paravesical approach with retrovesical and supravesical dissection forty-two times. Three cases have been encountered where extensive lateral attachment of the bladder to the lower uterine segment precluded any but a unilateral paravesical approach (two cases), or a supravesical approach (one case); these cases emphasize the importance of thorough knowledge not only of the anatomy involved but also of alternative techniques. The peritoneal staining technique⁶ used in twenty-nine operations decreased the incidence of technical accidents (Table III) and has had no deleterious effects.

TABLE III. INCIDENCE OF ACCIDENTAL OPENING OF THE PERITONEUM AND BLADDER IN SEVENTY-ONE CONSECUTIVE EXTRAPERITONEAL CESAREANS. USE OF THE PERITONEAL STAINING TECHNIQUE REDUCED BY ABOUT 50 PER CENT THE INCIDENCE OF ACCIDENTAL OPENING OF THE PERITONEUM

	NO. CASES	PERITONEUM OPENED		BLADDER OPENED	
		NO. CASES	PER CENT	NO. CASES	PER CENT
Peritoneum not stained	42	18	42.9	2	4.8
Peritoneum stained	29	6	20.7	1	3.4
Total	71	24	33.8	3	4.2

In a previous publication⁷ we outlined our technique for the bilateral paravesical extraperitoneal approach as carried out at that time.

We now prefer the Pfannenstiel incision, which gives adequate exposure for extraperitoneal cesarean and superior cosmetic results; and, except in the case of one patient with a previous midline suprapubic scar which we chose to excise, we have employed it in the last eleven consecutive operations.

We have eliminated any initial incision of the transversalis and perivesical fascias over the bladder as an unnecessary step. We now perform bilateral paravesical dissection directly, then retrovesical dissection with subsequent separation of the anterior and posterior transverse peritoneofascial folds and supravescical tissues from the bladder.

In the last five operations the urinary bladder was emptied by catheter and the catheter removed before operation. In the previous thirteen operations the catheter had been removed from the bladder immediately after operation. Of these eighteen patients, fourteen voided spontaneously.

Although our experience with the method is small, we have found thus far no disadvantage in performing extraperitoneal cesarean with neither fluid nor catheter in the bladder. Advantages are avoidance of the possibility of an obstructed catheter when it is desired to empty the bladder and diminished opportunity for urinary-tract infection.

Spinal anesthesia was employed for thirty-eight operations, general inhalation for thirty-one, local infiltration with intravenous Pentothal Sodium for one, and intravenous Pentothal Sodium supplemented with gas-oxygen for one.

Postoperative Course

There was no maternal mortality. Thirty-five patients exhibited postoperative febrile morbidity, having a temperature of 99.6° F., or more, an incidence of 49 per cent. Most morbidity was due to uterine sepsis and was mild in nature. There was one abscess of the abdominal incision which resolved promptly with drainage and one uteroabdominal fistula which closed spontaneously. Duration of febrile morbidity was one day in 13 cases, two days in 10, three days in 4, four days in 5, seven days in 1, nine days in 1, and thirteen days in one.

Two patients were afebrile, but may be considered morbid. One patient operated on in 1944 had an afebrile course, but after leaving the hospital developed an acute *Bacillus proteus* infection with sloughing of the bladder mucosa and subsequent bilateral hydroureter and recurrent attacks of pyelonephritis. The infection was traced to inept replacement of an indwelling catheter which became clogged about twenty-four hours after operation. As a result of this experience we have gradually eliminated catheterization as much as possible. A second patient exhibited a drainage sinus with serosanguineous exudate for five weeks.

Our present custom is to remove the urinary catheter before operation, to administer sulfonamide or antibiotic therapy for two or three days after operation or after the last catheterization, and to have patients ambulatory as soon as feasible—on the first postoperative day if their general condition permits.

Forty-nine patients have been available to us for postoperative examination four to six weeks after operation. Involution of the uterus in these cases was rapid and usually complete within four or five weeks. No case of subinvolution was observed. Six patients have been subsequently delivered by transperitoneal cesarean section, two of them twice; in all instances the peritoneal cavity was free of adhesions.

There were 4 infant deaths. Of 2 stillborns, one (Case 3 below) had been dead in utero for sixteen hours, the other was a 9-pound, 12-ounce infant exhibiting hepatosplenomegaly but no definite cause of death at autopsy. Of two neonatal deaths one was from hydrocephalus not diagnosed preoperatively, the other was a 3-pound, 1½-ounce infant delivered at 31 weeks' gestation because of placenta previa with hemorrhage and ruptured membranes for two days.

Case Reports

Of the cases in which the only reasonably safe alternative would have been cesarean hysterectomy or craniotomy, the following are briefly presented to show the value of extraperitoneal cesarean.

CASE 1.—Mrs. M. M., a 30-year-old primigravida at 41 weeks' gestation, demonstrated her inability to deliver vaginally after 34½ hours with ruptured membranes and 21½ hours of labor. During labor a sterile vaginal examination had showed the cervix to be completely dilated with the head high. After failed forceps, the patient was delivered on Nov. 17, 1941, by supravescical extraperitoneal cesarean of a male infant weighing 11 pounds (4,990 grams). One accidental opening of the peritoneum was closed by ligature. The patient exhibited an afebrile puerperium. Both patients were discharged in good condition on the twelfth postoperative day. This patient was subsequently delivered on Sept. 6, 1943, of a 7-pound infant by transverse cervical cesarean section. At the second operation there were no peritoneal adhesions.

CASE 2.—Mrs. H. P., a 24-year-old primigravida, exhibited severe pre-eclampsia at term, and cephalopelvic disproportion after 46 hours with membranes ruptured and 21 hours of good labor. One hour before section a sterile vaginal examination was performed, the cervix was almost completely dilated with an unengaged head and foul amniotic fluid; the patient's temperature was 100.8° F., the pulse rate 120. Supravescical extraperitoneal cesarean was performed on Feb. 13, 1943, and an 11-pound, 5-ounce (5,132-gram) female infant in good condition obtained. In the course of operation four small accidental openings in the peritoneum were closed by suture. The uterine contents were foul in odor. Five grams of sulfonamide powder were dusted over the extraperitoneal tissues. The patient exhibited morbidity for thirteen days and irrigation of the drainage tract, which was discharging pus, resulted in escape of fluid through the vagina. There was no evidence, however, of peritoneal irritation and the patient with her infant was discharged in good condition, with the sinus tract closed, on the seventeenth postoperative day.

CASE 3.—Mrs. J. N., a 23-year-old primigravida, experienced an uneventful pregnancy and went into labor at 40 weeks' gestation. After twenty hours of labor the fetal heart tones disappeared. The membranes were artificially ruptured at 11 A.M. on Aug. 7, 1948. Four hours later, because the patient had made no progress, she was seen in consultation by one of us. Examination disclosed a silent uterus contracting vigorously, foul amniotic fluid escaping from the vagina, and overlapping cranial bones presenting in a 5-cm. space between the symphysis pubis and a cystic tumor which occupied practically the entire true pelvis. The tumor produced absolute cephalopelvic disproportion necessitating abdominal delivery. Because of prolonged labor and the presence of foul amniotic fluid, delivery was performed by bilateral paravesical-supravescical extraperitoneal cesarean section at 4 P.M. Aug. 7, 1948. The bladder was inadvertently opened during operation and immediately repaired. Both catheter and drain were left in situ for seven days. The patient exhibited a foul lochia and purulent drainage from the incision. Total morbidity was four days, the highest fever being 103.2° F. on the second postoperative day when the patient experienced a chill during the course of a blood transfusion. Her subsequent course was uneventful and she was discharged from the hospital on the tenth postoperative day. The ovarian cyst was removed on Oct. 26, 1948, at a second operation from which the patient made an uneventful convalescence.

CASE 4.—Mrs. F. F., a 35-year-old primigravida, experienced a normal pregnancy except for an attack of right pyelonephritis during the fifth month. The membranes ruptured with the onset of labor at term on Nov. 14, 1948. After forty hours of labor when the cervix was 6-cm. dilated the caput was on the perineum. At this point it was felt that the patient would deliver vaginally. The obstetric situation had not changed ten hours later, however, and an attempt to deliver the infant with forceps after performing Dührssen's in-

cisions was unsuccessful. The head was tightly impacted in midpelvis. After 51 hours of labor with 51 hours of ruptured membranes, and failed forceps with Dührssen's incisions, a bilateral paravesical-supravesical extraperitoneal cesarean was performed on Nov. 16, 1948. There were no technical accidents. In order to deliver the baby it was necessary for an observer to dislodge the head from the pelvis with a sterile gloved hand and to assist in adjusting the forceps. A living male infant weighing 7 pounds, 13 ounces (3,544 grams) was obtained. After completion of the cesarean section the previously performed Dührssen's incisions were repaired. The catheter was removed after operation and the patient voided spontaneously. The drain was removed on the second postoperative day. The patient experienced no postoperative morbidity; both she and her infant left the hospital in good condition on the eleventh postoperative day.

CASE 5.—Mrs. J. G., a 27-year-old primigravida, was due by date on Sept. 18, 1947. Her pregnancy was complicated by pre-eclampsia for which she was hospitalized from September 26 to October 1 with improvement. She was readmitted on October 4 with ruptured membranes of two hours' duration, a few irregular labor pains, a temperature of 101° F., peripheral edema, and a blood pressure of 160/100. The labor pains subsided but in spite of adequate treatment the pre-eclampsia became more severe. X-ray showed an android pelvis with an unengaged head and borderline cephalopelvic disproportion. On Oct. 6, 1947, the amniotic fluid became foul and meconium stained; the temperature was 102.6° F. After thirty-six hours with membranes ruptured without labor the patient was delivered by bilateral paravesical-supravesical extraperitoneal cesarean of an 8-pound, 10-ounce (3,912-gram) female infant. The patient exhibited four days of temperature morbidity and was discharged from the hospital with her infant in good condition on the tenth postoperative day.

Summary

Seventy-one extraperitoneal cesareans performed between Nov. 15, 1941, and Jan 21, 1950, are reported. During this period no cesarean hysterectomies or craniotomies were performed for infected parturients. The indications for these operations are discussed. Recent modifications in technique and post-operative management concern principally the bladder. After preoperative catheterization the catheter is removed and operation is performed with the bladder empty. Postoperative catheterization is performed only when necessary. Mortality (0 maternal, 4 infant deaths) and morbidity (maternal, 49 per cent) experience is presented. Five of the cases in which the only reasonably safe alternative procedure would have been cesarean hysterectomy or craniotomy are briefly reported to emphasize the value of extraperitoneal cesarean section.

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AN IMPROVEMENT IN THE TECHNIQUE OF CONSTRUCTING THE VAGINA

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ONE of the basic requirements in constructing the vagina is the fixation of the skin graft so that it will take properly. It is equally important to fix the vaginal form securely so that the resulting vagina may be of large size.

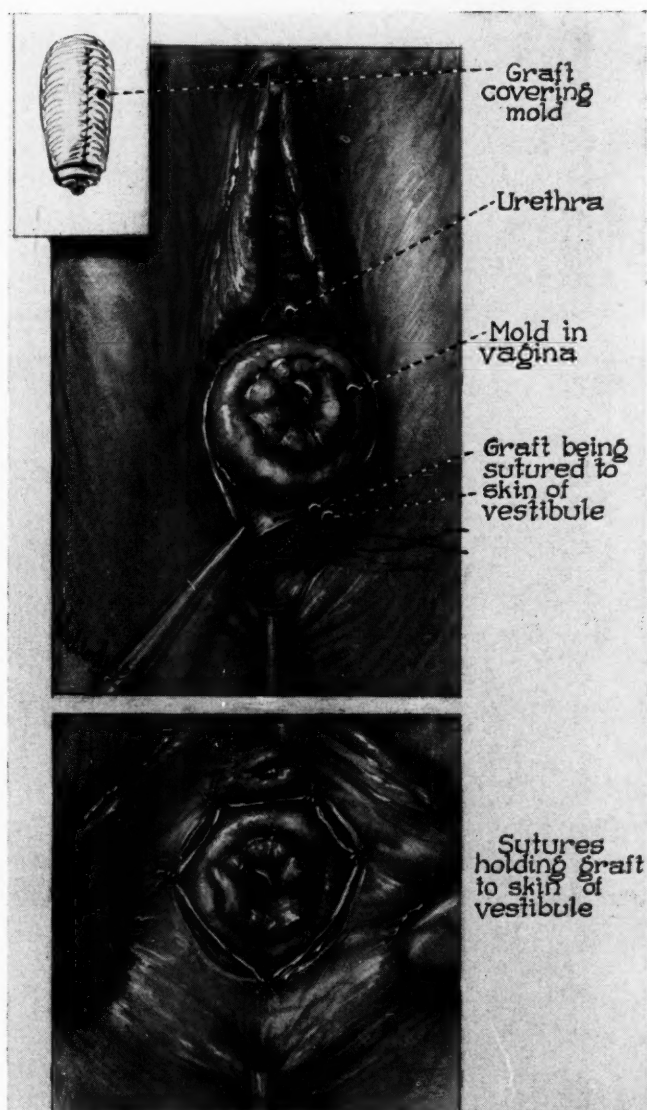


Fig. 1.—The new method of fixing the form and skin graft in the space dissected for the vagina. The edge of the skin graft is sutured to the cut edge of the vestibule by a few interrupted sutures of fine catgut. This allows adequate drainage and also prevents rotation and slipping of the graft and form.

To attain these objectives, various steps have been taken. In their original technique, McIndoe and Banister sutured the labia together over the end of the form, and this technique is still used by various English surgeons and occasionally in this country. We have never done this because we have found that



Fig. 2.—Vaginogram, taken five months after construction of vagina in December, 1948, shows a commodious and deep vagina. It measures 8 cm. deep above the vestibule.



Fig. 3.—The vaginal outlet in the preceding case, showing no deformity and a normal orifice.

sutures through the labia are often quite painful. Patients often complain even of the pain caused by sutures placed temporarily to hold the labia out of the way during operations for prolapsus. Hence, we have avoided suturing the labia over the vaginal opening to hold the vaginal form or grafts in place.

Others have used various sorts of binders and straps. These are cumbersome and do not fix the form or the grafts firmly or prevent rotation.

Shortly after the author performed his first operation for construction of the vagina in 1928, he attempted to ensure fixation of the form by making it conform to the shape of the vagina, with the inner end slightly larger than the outer. Perineal pressure on such a form would tend to push it further up into the vagina rather than outward. The author constructed these forms out of balsa wood.

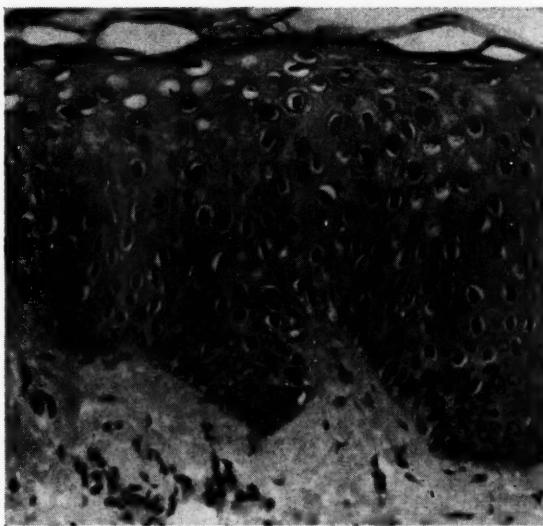


Fig. 4.—Biopsy of apex of vagina, 9 cm. above vestibule, taken one year after construction of vagina using technique described above. The vagina was 9 cm. deep and commodious.

Although these balsa wood forms have usually been satisfactory, the form has a good deal of "play" and, in one instance, was completely extruded with the graft, six hours after the operation. It is always necessary to watch these forms and to have the patient hold them in place while emptying the intestine or bladder. Thus, almost all the devices in current use have distinct disadvantages.

Three years ago, the author began to employ a simple step which seems to have solved this problem, at least in the cases in which we have used it. It consists merely in suturing the exposed edge of the graft to the cut edge of the vestibule. Both of these structures are tough enough to hold a few interrupted sutures of No. 000 chromic catgut. These are placed at regular intervals around the newly constructed vaginal orifice and completely fix both the graft and form, preventing either rotation or descent.

Fig. 1 illustrates this step. These sutures do not occlude the dissected space and allow adequate drainage. At the end of three weeks, the sutures have either been absorbed or loosened sufficiently so that the form can be slipped out easily. The graft stays in place. Also, by that time, the graft has taken so strongly that another form can be introduced without any inconvenience.

We are illustrating the actual step in Fig. 1, and in subsequent figures, the end result in two of the cases in which we have used this technique. Fig. 2 is a vaginogram taken five months after construction of the vagina. The vagina measured 8 cm. deep, was commodious, and showed no evidence of scar or contracture. It was lined by squamous epithelium. Fig. 3 shows the vaginal orifice in the case shown in Fig. 2. The orifice is normal, and the external genitals show no deformity or scar, such as follows some types of vaginal construction. Fig. 4 is a biopsy of the vagina in another case, one year after construction of the vagina, using the technique described in this article. The vagina measured 9 cm. deep, was large and completely lined by this type of normal squamous epithelium.

Summary

The author describes a new procedure, by means of which the skin graft and vaginal form are fixed in the space dissected for the vagina. The author has used this technique for the past three years, and has found it simple and satisfactory. He presents a follow-up study of two cases done since December, 1948. In one, the vaginogram shows a deep and commodious vagina, and the photograph shows a normal vaginal outlet. In the second case, the biopsy from the apex of the constructed vagina shows normal, healthy, squamous epithelium.

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MUMPS IN PREGNANCY

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IN RECENT years there have been numerous articles dealing with virus diseases occurring during pregnancy. It seems proved that rubella, if acquired by the pregnant woman in the first three months of her gestation, may cause congenital anomalies in the infant. Studies also suggest that not only rubella but any virus disease acquired by the pregnant patient in the first trimester of pregnancy can produce a defective offspring. The purpose of this paper is to give the author's experience with several cases of mumps in pregnancy.

Apparently little has been known about mumps as a complication of pregnancy, because the disease has been ignored completely in most of the obstetrical textbooks. Greenhill¹ stated that there was only one case of mumps in the Chicago Lying-in Hospital in almost 35,000 deliveries. Siddall² knew of one case in over 6,000 obstetrical patients. Recently several authors³⁻⁷ have reported cases in which a defective infant was born when mumps was acquired early in pregnancy.

During the winter of 1947 and spring of 1948 there were many cases of mumps in Chattanooga, Tennessee, and an occasional case is still seen. A number of pregnant women acquired the disease. The author had the opportunity of following nine cases; seven were his private patients, and two were service patients at the Baroness Erlanger Hospital.

Of the seven private patients, one multipara had mumps with a high fever during labor at term. She delivered a normal male infant spontaneously and without difficulty. Although it is stated that infants born when the mother has mumps may acquire the disease, this infant did not. The baby was normal in every respect, and at the end of a year has developed normally and without congenital defects. The mother made an uneventful recovery.

One primipara had a relatively severe case of mumps when she was approximately 36 weeks pregnant. The pregnancy continued to term, at which time the mother was delivered of a normal female infant. At the time of this writing, the baby is 3 months old, and appears normal in every way.

One primipara had a relatively mild case of mumps during the fourth month of her gestation. She was delivered at term of a normal female infant. This infant has been followed for over a year and has developed normally and without congenital defects.

One multipara acquired mumps during the third month of her gestation. She was delivered at term of a normal male infant. At the time of this writing, the baby is five months old and appears normal in every respect.

Another primipara acquired mumps during the second month of her gestation. She, too, was delivered at term of a normal female infant who has developed normally at the end of a year and without congenital defects.

One multipara, acquired a relatively mild case of mumps when she was approximately three weeks pregnant. There had been three previous pregnancies.

The first pregnancy was uncomplicated. Following the birth of her second child she developed phlebitis and pulmonary emboli. With her third pregnancy she had painless vaginal bleeding near term; a diagnosis of placenta previa was made, and she was delivered from below without great difficulty. All of the infants were normal. The author did not see the patient during these first three pregnancies. The fourth pregnancy, complicated by mumps, progressed in an uneventful manner until approximately one month before term. Then, suddenly in the middle of the night she developed typical signs and symptoms of an abruptio placentae. Without delay she was admitted into the hospital in mild shock. The fetal heart rate was 60. The patient was transfused and given intranasal oxygen. A pelvic examination soon after admission revealed the cervix to be long and closed. Consequently, a cesarean section was performed promptly; the uterine wall was moderately infiltrated with blood, but the uterus contracted well and was not excised. After a moderate amount of stimulation, the infant cried lustily and appeared normal. Both mother and infant had an essentially uneventful puerperium. At the end of one year the infant has developed into a bright, normal little girl, whom the author personally has seen. There are no malformations, and nothing to indicate that this child has been affected by the maternal mumps or the anoxia of the abruptio placentae.

One multipara, who had had considerable difficulty in conceiving, contracted mumps during the fourth month of her gestation. She aborted during her convalescence.

Of the two service patients, one had mumps during the first month of her gestation and one during the third month. The infants were born at term without congenital defects. A follow-up at the end of six months revealed them to be developing normally. A further follow-up could not be obtained.

The above nine patients were seen by reliable physicians, so there is every reason to believe correct the diagnosis of mumps. In addition to the above group, two service patients gave a history of mumps during the third month of their gestations. While their stories are probably correct, they were not seen by a physician, and hence the diagnosis cannot be verified. Both patients gave birth at term to normal infants without congenital defects.

Summary

Of eight patients who definitely had mumps during pregnancy and two who probably did, none had defective offspring. An eleventh patient aborted during her convalescence from mumps. This is in contrast to several cases reported in the literature, in which abnormal infants followed maternal mumps acquired early in pregnancy. In one of the author's patients, maternal mumps was followed later by an abruptio placentae.

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THE URINARY EXCRETION OF PREGNANEDIOL IN PREGNANT WOMEN RECEIVING DIETHYLSTILBESTROL

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ABNORMALITIES of progesterone metabolism as measured by the urinary excretion of pregnanediol have been described in a variety of obstetrical pathologies such as spontaneous and habitual abortion,¹ premature labor, maternal diabetes, and pre-eclamptic and eclamptic toxemia.² Because this abnormal laboratory observation may occur before clinical manifestations appear and often has prognostic significance, some have believed this alteration in progesterone metabolism to be pathogenic.³ However, this concept is still hypothetical, for attempts at direct replacement therapy with progesterone alone or estrogen and progesterone in combination have met with very limited clinical success.^{4, 5} It has since been advocated that these hormones be used prophylactically to prevent such accidents in the course of pregnancy.

Following the observation of Smith, Smith, and Hurwitz,⁶ that diethylstilbestrol increases the excretion of pregnanediol in the last two trimesters of pregnancy, this synthetic estrogen has been administered as a substitute for the more expensive and cumbersome estrogen-progesterone combination. Numerous reports of clinical success are appearing.⁷⁻⁹

It was the purpose of this study to measure the urinary pregnanediol excretion in patients receiving prophylactic diethylstilbestrol therapy and to compare the results obtained with our values for normal uncomplicated pregnancy. Only patients in whom the clinical results for mother and infant were excellent are included.

Method

Pregnanediol determinations were performed by the method of Astwood and Jones¹⁰ on twelve-hour collections of urine. The recommended technique was followed in every detail inasmuch as variations of the original technique, such as reducing the number of extractions with toluene, utilizing smaller initial volumes of urine, or utilizing colorimetric determination of the isolated pregnanediol, have yielded consistently lower results in our laboratory.

Urine samples were collected from the twentieth to the thirty-eighth week of pregnancy, and an average of eight determinations was performed on each of seven patients. All the patients received diethylstilbestrol according to the regimen suggested by Smith and Smith, and the medication was begun prior to the twelfth week of gestation. The following types of cases were utilized:

Habitual Premature Labor.—Three patients (two gravida iv and one gravida iii) who had a total of eight previous pregnancies resulting in the birth of premature living infants, none of whom survived the neonatal period. These patients had no living children.

Stillbirth.—Two patients (gravida ii), each of whom had delivered a still-born child in her previous pregnancy. The causes of these stillbirths were unknown to the attending physicians and were unexplained by postmortem examination.

Prepregnant Hypertension.—Both these patients were primigravidas. No exacerbation of their hypertension appeared during this pregnancy, nor were there any other clinical evidences of superimposed toxemia.

Results

A normal living full-term infant was delivered per vaginam in each case. All these infants survived the neonatal period. However, while the clinical results were excellent, no evidence of increased pregnanediol excretion was observed (Table I).

TABLE I. PREGNANEDIOL EXCRETION*
(mg. per 24 hours)

	PREGNANCY WEEKS									
	20-24		24-28		28-32		32-36		36-38	
	AVER.		AVER.		AVER.		AVER.		AVER.	
McC.	24.0 30.0	27.0	32.0 32.5	32.25	41.0 48.0	44.5	57.0 58.0	57.5	51.0	51.0
Dio.	23.5	23.5	32.0 44.5	38.25	58.0	58.0	68.0	68.0	62.5 68.5	65.5
Ner.	23.5	23.5	35.5	35.5	40.5 45.5	43.0	41.0 44.5 46.5	44.0	48.5	48.5
Can.	20.5 29.0	24.75	24.5 30.5	27.5	35.5 38.0 42.0	38.5	58.0	58.0	40.5	40.5
Ada.	24.5	24.5	30.0 34.5	32.75	32.0 33.0	32.5	38.0 42.0 50.0	43.3	51.0 70.0	60.5
Was.	21.0 23.0	22.0	33.5 35.5	34.5	47.0 50.0	48.5	62.5	62.5	57.0	57.0
Fra.	21.0 22.5	21.75	30.0	30.0	31.0	31.0	36.0 42.5	39.25	40.5	40.5
Aver. diethylstilbestrol treated cases	24.0		33.0		42.5		53.5		52.0	
Aver. normal untreated cases†	25.0		34.0		43.0		51.0		54.0	

*In recovery experiments, 68-72 per cent of the theoretical value of pregnanediol was obtained for quantities ranging from 5-100 mg. of sodium pregnanediol glucuronide added per liter of male urine. The values expressed in this table are calculated by the formula, Calculated Value = Measured Value/0.7.

†One hundred determinations were performed on 12-hour urine specimens of 20 normal pregnant women. The figures tabulated represent the average result for each period of gestation.

Comment

This is the fourth report to appear concerning the urinary metabolites of progesterone in pregnant women receiving diethylstilbestrol. The original investigation of Smith et al. indicated increased excretion of pregnanediol. This experimental result could not be duplicated by Davis and Fugo.¹¹ The subsequent work of Sommerville and Marrian demonstrated decreased excre-

tion of pregnanediol.¹² In each instance, the diethylstilbestrol was given for only a short period of time, and its effect was noted in individual patients before, during, and after therapy. This present study differs from those listed above in that the drug was administered over a prolonged period of time, in increasing dosage and in the usual therapeutic manner. Furthermore, we have compared potentially abnormal cases receiving therapy with normal untreated patients.

Each of these four studies was concerned with the measurement of pregnanediol and each investigation utilized a different technique for the measurement of this compound. It has been demonstrated that the method of Venning and Browne, used by Smith and Smith, measures not only pregnanediol and its isomers, but also a pregnanolone.¹³ This latter substance represents about 20 per cent of the material assayed by the Venning and Browne technique, but is not recovered in the procedures utilized by Sommerville, Davis and Fugo, or ourselves. Therefore, while one may conclude that diethylstilbestrol does not increase pregnanediol excretion, one may not infer at this time that this synthetic estrogen has no influence on other urinary metabolites of progesterone.

Summary

1. Urinary pregnanediol determinations were performed by the method of Astwood and Jones, during the twentieth to the thirty-eighth week of pregnancy, on seven women receiving prophylactic diethylstilbestrol therapy.

2. No increase in pregnanediol excretion was observed.

3. This result indicates that diethylstilbestrol has no stimulating effect on progesterone metabolism *as measured by pregnanediol excretion*.

The author gratefully acknowledges the able technical assistance of Phyllis Wood, A.B.

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THE BACTERIAL FLORA FOUND IN NONSPECIFIC VAGINAL DISCHARGE

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GYNCOLOGICAL examination of institutionalized women by one of us (J. D. W.) revealed a considerable number of cases of vaginal discharge which could not be ascribed to an infection with either the gonococcus, *Monilia* or *Trichomonas*, nor to a malignancy. Little seems to be known about other possible incitants of vaginal discharge, since much of the work on the flora of the female reproductive tract has been concerned with normal individuals, or with some special organism or group of organisms, and the organisms isolated have not been identified to species in all instances. The pathological significance of any one of the types present in a normal person is uncertain, but the fact that types similar to those present in pathological conditions, apparently as the causal organism, are found has led to the concept of endogenous infection, and has stimulated interest in the female reproductive tract as a possible portal of entry for pathogenic bacteria. It appeared that a qualitative determination and species identification of the flora present in these cases of nonspecific vaginal discharge might possibly have more than casual interest, and accordingly the study here reported was undertaken.

Curtis,³ from a study of the origin and cause of leucorrhea, believed the anaerobic vaginal flora to be of paramount etiological importance, and since the gram-negative bacilli were in greatest proportion he ascribed most significance to this group. Döderlein's bacillus and gram-positive diplococci were constantly present but were never predominant. He thought it doubtful if colon bacilli, when present, participated actively in the pathologic change. Maryan⁸ isolated 41 stains of gram-positive cocci of low virulence from 51 cases of chronic cervicitis. He considered these to be enterococci. Ten of the patients gave negative cultures.

Schroder⁹ established three groups of individuals on the basis of the nature of the vaginal flora, and considered these to correspond to the degree of cleanliness. Group 1 showed only Döderlein's bacillus; Group 2 had a mixed flora with Döderlein's bacillus in the minority, and Group 3 had a mixed flora with no Döderlein's bacillus present. Carter and Jones² added *Staphylococcus albus* and yeast to Group 1. They were in agreement with Schroder as to Groups 2 and 3. Döderlein's bacillus, which has long been regarded as a common inhabitant of the female reproductive tract, was not recovered by them from 70 per cent of the gynecologic or 44 per cent of the obstetrical patients. Other isolations by these investigators included, with some degree of frequency, anaerobic streptococci, gamma streptococci, alpha streptococci, *Escherichia coli* and, infrequently, several other rods and cocci, including on two occasions the

black-pigmented coccus of Colebrook. The frequency with which anaerobic streptococci were found appeared to be unaffected by the incidence of yeasts and Döderlein's bacillus, but gamma streptococci decreased with an increase in these aciduric organisms.

Hite, Hesseltine, and Goldstein⁵ presented results from normal pregnant persons similar to those noted by Carter and Jones. The most frequently encountered types included aciduric rods, diphtheroid rods, *Staphylococcus albus* and fungi of both monilial and yeastlike types. Nonhemolytic streptococci and anaerobic streptococci were isolated frequently. In patients with trichomoniasis there was an increased frequency of both aerobic and anaerobic streptococci, and of members of the bacteroides group, with a lesser frequency of aciduric rods. They state that the cultural results from patients with vaginitis associated with some gynecologic condition differed only slightly from those from normal persons. Their cultural results from febrile and postabortal puerperas were very similar to those from normal postpartum women, and from endometritis patients. A detailed bacteriologic study of 92 strains of aerobic streptococci isolated during the process of this work was reported by Hite and Hesseltine.⁴

The present report gives the bacteriologic findings in cultures from 52 cases of abnormal vaginal discharge, and from 10 persons living under identical environmental conditions, but showing no discharge or other evidence of vaginitis.

Materials and Methods

Patients and Controls.—

The patients who were cultured consisted of 52 inmates of the Texas State Hospital at Austin who earlier had been found to have an abnormal vaginal discharge. Cultures for *Neisseria* and *Monilia albicans*, and wet preparations for *Trichomonas vaginalis* had been made at the time of the first examination. Biopsies of every cervix, and fresh smears for uterine cancer had been done in all cases. The individuals included in the present series were only those in whom the cause of the discharge remained undetermined. Three treated cases of *Trichomonas* infection in which a discharge persisted after negative smears were obtained, and two cases of *Trichomonas* infection in which it was believed the discharge was due to some other factor than the *Trichomonas* have been included. All of the patients were adults, the majority being between 45 and 55 years of age. Three showed an intact hymen. None was pregnant.

Seventeen members of the test group showed no obvious diseased condition other than the discharge. Among the other 35, one or more gynecological abnormalities each were recorded, as follows: vulvitis, 8; vaginitis, 7; cervicitis, 10; endocervicitis, 1; lacerated perineum, 10; lacerated cervix, 9; ulceration of cervix, 2; erosion of cervix, 4; hypertrophy of cervix, 2; malignancy of cervix, 2; vaginal atrophy, 5; vaginal ulceration, 1; chronic salpingitis, 1. Nine of the group showed a discharge classed as scanty in amount, 24 moderate, and 19 profuse. The character of the discharge showed considerable variation. Descriptive terms applied at the time of culturing include thin white, creamy yellow, yellowish green, mucopurulent, brown, foamy, white caseous, creamy white, yellowish white, etc. The pH values as determined by the use of nitrazine paper were recorded as follows: 4.5 in 11, 5.0 in 4, 5.5 in 1, 6.0 in 4, 6.5 in 3, 7.0 in 16, 7.5 in 12. No correlation between character, amount, and pH of discharge was apparent.

Although the 10 controls were free of discharge, 7 of them showed some gynecological abnormality as follows: hypoplastic uterus, 1; retroversion of uterus, 4; prolapse of uterus, 1; laceration of cervix, 1; lacerated perineum, 1; erosion of cervix, 1; laceration of vagina, 1; hypertrophy of labia, 1. One of the controls had an intact hymen.

The pH values established by touching nitrazine paper to the vaginal wall were as follows: 5.0 in 1, 6.0 in 2, 7.5 in 7.

Media.—

The variety and types of bacteria which have been recorded for the vaginal area emphasized the importance of a careful selection of media and of cultural environmental conditions. In order to meet the growth requirements of some of the types which were certain to be present an enriched medium is necessary. Experience has established the value of the Bacto GC medium base with 1 per cent hemoglobin, 1 per cent supplement B, and 0.1 per cent glucose for the isolation of fastidious organisms of urogenital origin, and consequently this was the medium used for the aerobic and microaerophilic types. For anaerobic types, 5 per cent whole blood was substituted for the hemoglobin and 0.02 per cent sodium thioglycollate was added. Eosin-methylene blue medium was used to detect members of the enteric group, and tomato juice agar (Kolmer and Boerner⁶) adjusted to pH 6.8 for aciduric organisms. Clay tops were used on the dishes and all were incubated for sterility before use.

Culture Methods.—

A cotton swab inserted through and ahead of a sterile bivalve speculum was used to obtain material for culture from the area around the cervix. Plates were inoculated by rolling the swab over a small section of the surface of the medium and streaking out so as to secure isolated colonies.

For a time smears for staining by Gram's method were made from the swab, but when it became evident that because of extreme pleomorphism the stained preparations gave little or no indication of what would be found in the cultures this part of the procedure was discontinued.

All cultures were incubated for 48 hours at 37°C. The eosin-methylene blue and tomato juice media were incubated aerobically. The hemoglobin medium was incubated in a candle jar, and the anaerobic plates in an oat jar with methylene blue as an indicator of anaerobiosis. Transplants of each colony type were made to tubes of the medium used for primary isolation. The isolates were identified according to *Bergey's Manual of Determinative Bacteriology*.¹ Organisms identified culturally as *Corynebacterium diphtheriae* were tested for virulence by guinea pig inoculation. The strains of *Klebsiella pneumoniae* were typed with Lederle typing sera.

Results

Twelve species distributed among five genera were recovered from the test series and not from the controls. Nine species, representing eight genera, occurred in both the test series and the controls. The frequency of isolation and the percentage of the patients showing each of the 21 species recorded are given in Table I. Percentage figures for the controls are not recorded because of a lack of significance due to the small numbers.

It may well be questioned whether the members of the enteric group, *Esch. coli*, *A. aerogenes* and *K. pneumoniae*, and also *Proteus morganii*, *A. faecalis* and *Ps. aeruginosa*, really represent true vaginal flora or, as would seem more likely, are adventitiously present. There is less uncertainty about the other species, although *Sarcina* and *Gaffkya* possibly should be viewed with some suspicion. The number of times *Klebsiella* was isolated emphasizes the fact that this organism is not restricted to the respiratory tract, but may be encountered in other habitats as well.

It will be noted that no beta hemolytic streptococci were encountered, and that the incidence of anaerobic streptococci was fairly low. The most frequently encountered species, which was identified as *Micrococcus epidermidis*,

was recovered from 32 of the test series and 7 of the controls. Second in frequency in the test series was *Str. faecalis*, but this type was isolated from only one of the controls. *Corynebacterium* species occurred fairly commonly among both patients and controls. No *Bacteroides* were recovered from controls, although 19 strains divided between two species were isolated from the test group.

The frequency with which *Neisseria* species was isolated is noteworthy. In over 40,000 cervical cultures Lankford⁷ found less than 0.1 per cent of the individuals to show *Neisseria* other than the gonococcus. It has been the experience of one of us (J. D. W.), however, that *Neisseria* species occur with a relatively high degree of frequency among institutionalized females. It may be that the occurrence of this genus is a consequence of the institutional life of the individuals examined.

Of especial interest is the fact that no smears were suggestive of the presence of the Döderlein bacillus, and no cultures of it were recovered from either patients or controls. An explanation of this finding may possibly be in the failure to incubate the plates of tomato juice medium under either anaerobic conditions or increased carbon dioxide tension. However, in view of the fact that none of the stained smears showed rods suggestive of this organism, the failure to secure growth of an aciduric in the primary cultures was not altogether unexpected. Furthermore, in the experience of one of us (O. B. W.) aerobic growth in primary cultures of several aciduric types on tomato juice medium has been regularly obtained, although somewhat less luxuriant than under microaerophilic conditions. Certainly if aciduric types were present at all they were not abundant.

TABLE I. FREQUENCY OF ISOLATION OF VARIOUS BACTERIAL SPECIES

ORGANISM	NUMBER OF TIMES ISOLATED AND PERCENTAGE FREQUENCY		
	NO. PATIENTS	%	NO. CONTROLS
<i>Aerobacter aerogenes</i>	2	3.9	1
<i>Alcaligenes faecalis</i>	11	21.1	
<i>Bacteroides fragilis</i>	13	25.0	
<i>Bacteroides melaninogenicus</i>	6	11.5	
<i>Corynebacterium acnes</i>	3	5.8	
<i>Corynebacterium diphtheriae</i> (nontoxic)	3	5.8	
<i>Corynebacterium enzymicum</i>	15	28.7	1
<i>Corynebacterium pseudodiphtheriticum</i>	12	23.0	6
<i>Escherichia coli</i>	10	19.2	3
<i>Gaffkya tetragena</i>	3	5.8	1
<i>Klebsiella pneumoniae</i> type B	7	13.5	
<i>Micrococcus epidermis</i>	32	61.5	7
<i>Micrococcus pyogenes</i> , var. <i>albus</i>	4	7.7	
<i>Neisseria flava</i>	1	1.9	
<i>Neisseria perflava</i>	5	9.6	
<i>Neisseria subflava</i>	3	5.8	1
<i>Proteus morgani</i>	5	9.6	2
<i>Pseudomonas aeruginosa</i>	1	1.9	
<i>Sarcina flava</i>	3	5.8	
<i>Streptococcus anaerobius</i>	5	9.6	
<i>Streptococcus faecalis</i>	31	59.6	1

In considering the results as a whole, it hardly appears suggestive that any one or more types bears a cause-and-effect relationship to nonspecific vaginal discharge. There was no evidence of a correlation between the character or amount of the discharge and any particular organism. On the basis of the results obtained in the work it appears unlikely that nonspecific vaginal discharge has a bacterial etiology.

Summary

Bacteriological examination of nonspecific vaginal discharge yielded twenty-one species of bacteria, nine of which occurred also in controls. There did not appear to be a relationship between the presence of any one or more of the organisms and the discharge.

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VAGINAL MYCOSIS IN PREGNANCY: AN IMPROVED GENTIAN VIOLET TREATMENT

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VAGINAL moniliasis is a major nuisance of pregnancy. There is nothing in laboratory or clinical findings or history to label it a major threat, or even one occasionally associated with life-endangering complications. Excluding neonatal oral thrush, pathologically, little can be ascribed to it. It is self-curative for it occurs almost exclusively (not completely) in pregnancy and disappears largely by the fifth postpartum day. It will persist or appear in diabetics, in some postmenopausal "overtreated" women, and some cases of hyperestrinism. It is difficult to cure, for the fungal hyphae grow into the epithelial layers, the conidia and spores are resistant to varying therapy, and recurrence is common. The variety of applications suggested for treatment is evidence enough of need for an adequate means for easy control, if not cure. Of the many, gentian violet is the one most commonly referred to, used, and returned to, and the favorite of most gynecologists. It is with a new form of gentian violet application that this communication deals.

Material and Methods

The material used is gentian violet in an acid polyethylene glycol base* prepared according to the formula:

Gentian violet	0.2%
Lactic acid	3.0%
Acetic acid	1.0%
Polyethylene glycol	q.s.

Our initial preparation contained 1 per cent gentian violet, promptly reduced because of the marked excoriative effect. The balanced preparation was finally achieved by clinical and laboratory observance of toleration and effectiveness. For the latter, the test organism was *Candida albicans*. Serial dilutions of the jelly were prepared in brain-heart infusion and seeded with a 1:10 diluted *Candida albicans* broth culture. Growth was read after incubation at 37° C. for 24 hours. The results indicate that at a dilution of the jelly of 1:13,500 complete inhibition was obtained. Partial inhibition was obtained at a dilution of 1:40,500. A dilution of the jelly of 1:13,500 represents a dilution of the contained gentian violet of 1:675,000. Karnaky disagrees with the belief that mycotic infestations are best treated with alkaline preparations and has shown that these organisms grow at any pH. In addition, acid media inhibit the growth of other pathogenic organisms and secondary infectors accompanying vaginal moniliasis and a suitably buffered acid medication is therefore preferable.

To obtain a form of application usable in clinic and home, and to avoid the inconvenience and soilage of the purple smear associated with gentian violet, the single-dose disposable applicator described by Siegler was used. The 0.2 per cent gentian jelly proved to be nonirritating to the genital membranes without sacrifice of effectiveness, and was the final choice for therapy evaluation using single-dose disposable applicators.

*Supplied by Westwood Pharmaceuticals, Division of Foster-Milburn Co.

Incidence of Mycotic Infection

Hesseltine and Beckett estimate conservatively that 25 per cent of all gravid women harbor the *Candida albicans* organism in the vaginal secretions and that a fair percentage will develop mycosis. Gardner found *Candida albicans* in 11.5 per cent of 585 obstetric patients, while Karnaky reported its presence in 15.5 per cent of 2,000 pregnant women on whom smears were taken routinely. In contrast, Gardner observed the organism in only 2.85 per cent in a group of 491 nonpregnant patients, and Karnaky in 3.5 per cent in 20,000 women examined gynecologically. Two hundred five gravid patients at the Margaret Hague Maternity Hospital were treated. Their ages ranged between 18 and 38 years, and, except for the moniliasis detected, they were regarded as normal.

Most of these patients were in the last trimester of pregnancy, complained of the classic symptoms—itching, burning, discharge, local tenderness, dyspareunia—and presented physical findings suggesting monilial vaginitis. Confirmation was obtained by microscopic examinations of saline suspensions of material swabbed from the vagina and brain-heart incubated infusion.

Of the 205 patients started on treatment, fourteen were lost either by transference to private physicians, failure to return, or delivery before evaluation of results.

Upon laboratory confirmation of the diagnosis, each patient was given twelve single doses of the gentian violet jelly, and was instructed in home application of one dose daily at bedtime. A perineal pad was advised to prevent staining and yet permit some contact of the jelly with the vulva and perineum. Each patient was seen at the end of two weeks. Criteria for determining a cure were complete remission of symptoms, absence of visible vaginitis, and three negative tests for *Candida albicans* taken at two-week intervals after stopping therapy.

Further courses of twelve doses were given in each case, if the complete criteria for a cure were unfilled.

Results

Table I illustrates the results obtained. Of the 191 cases with complete data, 149 (78 per cent) were considered cured. In 23 (12 per cent) the smears became negative but symptoms, although improved, were not completely absent. In 5 (3 per cent) the symptoms improved but the smear remained or subsequently became positive. Fourteen (7 per cent) were unimproved, with persisting symptoms and positive smear.

TABLE I. RESULTS OBTAINED IN TREATING 191 GRAVID PATIENTS WITH MYCOTIC VAGINITIS

DURATION OF TREATMENT	CURED		SMEAR BECAME NEGATIVE BUT SYMPTOMS ONLY IMPROVED		SYMPTOMS IM- PROVED, BUT SMEAR REMAINED POSITIVE		NO RESULTS	
			NUMBER	PER CENT	NUMBER	PER CENT		
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
	149	78	23	12	5	3	14	7
0-2 weeks	129	87	17	75	3	60	8	57
2-4 weeks	17	11	3	13	2	40	3	22
Over 4 weeks	3	2	3	13	0	0	3	21

A noteworthy observation was the rapid symptomatic response to the therapy employed. Itching and burning were frequently controlled within 48 to 72 hours after the first dose. Genital tenderness disappeared promptly.

Of the 149 patients listed as cured in Table I, 129 (87 per cent) needed only one course of treatment, i.e., twelve doses over a period of two weeks. Seventeen (11 per cent) required twenty-four doses over a period of four weeks, and more than four weeks of therapy were necessary in only 3 (2 per cent).

Comment

Mycotic infections are difficult to control in the gravid patient, especially during the last trimester of pregnancy. Branscomb, utilizing a propionate jelly, was unable to effect a cure in her pregnant patients, whereas, with the non-pregnant, 64.7 per cent were cured at the end of three weeks. Jones and associates, also using a propionate jelly, were able to cure 80 per cent of the non-pregnant patients but only 33 per cent of those pregnant. Allen and Baum, using a ricinoleic-acid jelly, obtained 71 per cent cures in nonpregnant women and 52 per cent in those pregnant. With Hesseltine and Beckette, cures in the nonpregnant were 90 per cent, whereas in the pregnant they were only 74 per cent.

The results in this series of pregnant patients, 93 per cent combined cures and improvement, and 7 per cent complete failures, compare favorably with those achieved by any reported method and support the long-held belief that gentian violet is specific for mycotic infections of the vagina.

The acid polyethylene glycol gentian violet jelly in single-dose disposable applicators overcomes most of the disadvantages associated with usual gentian violet therapy and permits self-treatment until term or onset of labor. A residual disadvantage when using any form of gentian violet is conjugal purpling after coitus. But during the last trimester of pregnancy intercourse should be restricted and, in our experience, there are few greater deterrents than the therapy used, both practically and psychologically.

Summary

Gentian violet is still the most consistently effective therapy we have employed in vaginal mycosis.

A new jelly is described, packaged in single-dose disposable applicators, and eliminating the disadvantages associated with other gentian violet applications.

In a series of 191 pregnancy cases, cure was obtained in 78 per cent, improvement in 15 per cent, and failure in 7 per cent.

In 87 per cent of those patients considered cured, treatment consisted of one course of twelve doses given over a period of two weeks. In 11 per cent, using twenty-four doses, treatment covered a period of four weeks.

We wish to express our gratitude for the laboratory assistance rendered by Ray Chesley, Bacteriologist at the Margaret Hague Maternity Hospital.

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EFFECTS OF DEXEDRINE SULFATE ON NAUSEA AND VOMITING OF PREGNANCY

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THEORIES advanced to explain the nausea and vomiting of pregnancy range all the way from simple hunger to complex hormonal changes. Stander,¹ in a recent review of the subject, mentions at least a dozen hypotheses, including the development of various antigens, overirritability of the vagus, and an increase or decrease in the activity of several organs and glands. Obviously, there is as yet no agreement on what the basic cause of this condition may be.

There is probably little disagreement, however, that certain conditions often aggravate nausea and vomiting. Psychic factors almost surely are influential. There may be fear of pregnancy, response to suggestion by friends or relatives who have experienced morning sickness, or simply a desire for attention and sympathy. On the positive side, the very fact that so many therapies have at least some degree of effectiveness confirms the importance of psychological influence. A second pertinent factor is the increased appetite usually experienced in pregnancy. Hunger alone can produce nausea; and the woman who, for whatever basic reason, cannot tolerate the odor or sight of food or vomits food she eats, becomes voraciously hungry. She is then not only caught in a pattern of hunger-nausea-vomiting-hunger, but becomes weak, discouraged, and more susceptible to emotional influences.

For the past year or so we have been getting excellent symptomatic relief of nausea and vomiting simply by trying to eliminate these aggravating factors. Quite by accident, originally, we noted that d-amphetamine sulfate, or Dexedrine sulfate, which is well known for its psychic and antiappetite effects,^{2, 3, 4, 5} shows promise in controlling nausea and vomiting. It happened that a patient who had been unable to retain any food for a week was, for personal reasons, faced with the necessity of attending a dinner. She requested something to control her appetite, on the grounds that the constant sensation of gnawing hunger in itself made her nauseated and she might feel somewhat better if she were not tempted to eat. Questionable as this seemed at the time, she was given a Dexedrine tablet to take an hour before the event. The next day she reported that she had not only been free of nausea before the meal, but had found it possible to eat a fair-sized dinner with no ill effects. Furthermore, instead of being discouraged and apprehensive, she had felt quite well and vivacious. She wanted to continue the drug, and since Dexedrine had been shown to produce no ill effects on either mother or child when used during pregnancy⁵ there seemed no reason to refuse. From that time on she had no further difficulty with nausea and vomiting.

An isolated case of this sort might well be merely coincidence or an example of the result of suggestion. Nevertheless, the prompt and sustained relief was

interesting. On thinking over the actions of Dexedrine as applied to the type of woman most susceptible to nausea and vomiting, the treatment appeared to have some rational basis. It was decided to try Dexedrine therapy in some other patients with nausea and vomiting of pregnancy, to see if it produced any consistent results. To date, we have used this treatment in 165 cases, which are the subject of this report.

Method

The patient was instructed to take a 5-mg. tablet of Dexedrine sulfate on awakening, or one hour before breakfast, for three days. This single daily dose was used at first because many of the women subject to nausea and vomiting are of nervous temperament and might possibly show an exaggerated response to a stimulant. If no undue nervousness was reported, however, another 5 mg. one hour before lunch were prescribed. The dosage was varied slightly when indicated. Some patients who were overstimulated by the second 5 mg. responded well when this dose was cut to 2.5 mg. An occasional patient required a third tablet around 3 o'clock in the afternoon; the drug should not be taken much later as it may cause insomnia, but if necessary this can be controlled by a small dose of a barbiturate. We also instructed the patient to take small, frequent meals during the first trimester.

The treatment was considered successful if symptoms were completely relieved within ten days, i.e., if by that time both nausea and vomiting were completely controlled, and did not recur. When complete relief was obtained, the patient was given ascorbic acid tablets instead for three days as a crude sort of control designed to rule out any purely psychological response.

Results

Of the 165 patients treated with Dexedrine, 148, or 90 per cent, obtained complete and lasting relief. However, since 13 of these 148 patients continued to be free of nausea and vomiting when ascorbic acid was substituted for Dexedrine, they should probably be regarded as suggestible persons who might respond to any therapy. With the omission of these cases, the total of successful results with Dexedrine is 135, or 82 per cent.

Response to Dexedrine therapy followed a clear pattern. In almost every case (156 of the original 165) there was distinct improvement within three days. These patients still had some nausea and vomiting, but it was much less frequent and severe. Within four days, 99 of the patients had ceased vomiting entirely, although there was not complete freedom from nausea. It might be noted that this cessation of the more distressing symptoms coincided with the time when the higher dosage of Dexedrine was adopted (following the three-day "test" period on 5 mg. a day). Cessation of all symptoms occurred at the earliest on the fourth day; half the patients had complete relief within a week. Since 90 per cent of the patients were entirely free of symptoms by the tenth day, the remaining cases were regarded as failures and were given other treatment.

The failures, 17 cases, ultimately responded to treatment with Nembutal suppositories, hospitalization, or simply time. Of this group, 8 were in the 4-plus classification, i.e., vomiting all ingested food and liquids over a 48-hour period. None of the patients with this degree of nausea and vomiting responded to Dexedrine therapy.

No serious side effects were observed with this treatment. About 15 per cent of the patients complained of nervousness, but this was usually overcome by decreasing the dosage or prescribing small doses of phenobarbital. Treatment was continued through the entire first trimester without any unusual developments. Like others^{5, 6} who have prescribed Dexedrine during pregnancy, we noted no untoward effects at delivery in either mother or child.

Comment

As far as the effectiveness of Dexedrine goes, our results in this series require little comment. The percentage of favorable responses is high enough to make Dexedrine appear to be very satisfactory therapy. We do not mean to imply that this figure is unprecedented. Finch,⁷ for example, reported a higher percentage of good results with antihistamine therapy. We, too, have found Dramamine, Benadryl, and such drugs of definite value in controlling these symptoms, but in our experience the accompanying drowsiness was sometimes so alarming that use of this therapy did not seem warranted. Incidentally, the frequent occurrence of this side effect has led us to wonder if some of the effectiveness of the antihistamines in this condition might not be due primarily to sedation. Like many others, we have always found the barbiturates helpful in nausea and vomiting, and some of our best results have been obtained with Nembutal suppositories or oral phenobarbital. Effective as they are, however, sedatives have recognized drawbacks, for they increase the lethargy and depression which many women experience during pregnancy.

The great advantage of Dexedrine for treatment of nausea and vomiting lies in its stimulant action. Instead of somnolence, it produces alertness; and it elevates, rather than depresses, the mood. In this series, 80 per cent of the patients—almost the entire number benefited—spoke of getting a “lift” from the drug. For the housewife who must continue to care for her family during the period of gestation, this is an important attribute.

We do not wish to leave the impression that we regard Dexedrine as the final answer to nausea and vomiting of pregnancy. That will not be found until the etiology is clearly established. We have no theories to offer on why Dexedrine should produce such good results beyond those that suggested themselves before this study was undertaken: that it eliminates aggravating psychic and hunger influences. In connection with the antiappetite effect, it is interesting to note that there is some evidence that Dexedrine decreases olfactory acuity.^{4, 8} Such an effect would be added help to those patients who are disturbed even by the odor of food. In any case, Dexedrine appears to be valuable symptomatic treatment, with several advantages over other therapies for nausea and vomiting of pregnancy. To recapitulate, it usually gives prompt and lasting relief; it is effective orally; it produces no significant side effects; and it gives mental and physical stimulation which improves the patient's morale and enables her to carry on normal activities.

Summary

1. In a series of 165 patients with nausea and vomiting of pregnancy, Dexedrine sulfate produced complete relief in 148, or 90 per cent. On substitution of a placebo, 13 of these patients remained free of symptoms; omitting these suggestible patients, the final satisfactory cases number 135, or 82 per cent.

2. Marked improvement occurred in almost every case within three days. Within four days, 99 of the patients had ceased vomiting, but still had some sensations of nausea. Complete relief occurred in four to ten days. The only side reaction observed was nervousness which was easily controlled by reducing the dosage or by prescribing small amounts of barbiturates.

3. The effectiveness of Dexedrine is probably due to its mood-elevating and antiappetite actions. While it is not basic therapy, Dexedrine has definite advantages over other treatments, most important of which are the mental and physical alertness, and the general feeling of well-being which it produces.

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105 OSLER BUILDING

EXPERIENCES WITH PSP TUBAL PATENCY (SPECK) TEST

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DURING the routine performance of phenolsulfonphthalein tubal patency (Speck)¹ tests upon patients whose pelvic organs later became available for study, a lack of correlation between the test results and the condition of the tubes was noted. A group of patients was then studied to determine more accurately the validity of our first impression.

This series consisted of 25 patients whose pelvic organs could be carefully examined by the surgeon at the time of operation and in the laboratory by various members of the Department of Pathology. The PSP test was done on the day prior to operation on patients with adnexal or uterine lesions.

The technique followed was that of Speck. PSP is instilled into the uterine cavity and, at the end of 30 minutes, the bladder is catheterized. According to Speck, if the urine turns red or pink when alkalinized, the tubes are considered patent; if there is no discoloration, closed. The test is based upon the premise that PSP is not easily absorbed from the normal vaginal mucosa, endometrium, or endosalpinx, but is readily absorbed from the peritoneum.

Details of the procedure are as follows: Sterile technique is employed. The bladder is emptied and a bivalve speculum is inserted into the vagina. The cervix is then grasped with a tenaculum and the uterus sounded. A uterine cannula with a stopcock at the distal end is filled with PSP solution (12 mg. or 2 c.c. of PSP solution added to 20 c.c. of isotonic saline) and inserted into the uterus. A 20-c.c. syringe containing the remainder of the PSP solution is connected to the cannula and 10 c.c. of the solution are slowly injected. The stopcock in the system is then closed so that there will be no reflux of the solution. The patient drinks eight ounces of water at this time. The cannula is removed in 10 minutes, a tampon placed in the vagina, and the patient kept flat on the table for an additional 20 minutes. At the end of this time, the bladder is catheterized and 10 per cent sodium hydroxide added to the urine. If the urine turns pink or red, the tubes are considered patent; if there is no change in color, the tubes are considered nonpatent.

In this series of cases, modification of the test was necessary, so that less than 10 c.c. were injected through the cannula when it became obvious that too great pressure was being exerted. In fact, we could sense the presence of blocked tubes by the resistance encountered, by the tendency for and the amount of reflux, as well as by the subjective response of the patient to the distended uterus and tubes. On other occasions, more than 10 c.c. were injected, especially when the uterus had a sounded depth of over 4 inches.

Further modification involved the end point or concentration of color. The criteria used in the first eighteen cases were those used by Speck: "If the urine turns pink or red, the tubes are considered patent; if there is no discoloration, closed." In the last seven cases, the suggestions of Israel and Freed,² who made quantitative determination of the urinary content of PSP, were followed. They

found that violet pink to pinkish color occurred in alkalinized urine when it contained less than 5 per cent of the PSP, and a deeper pinkish hue appeared as 5 per cent was approached. We noted that red coloration was definite when the urine contained over 10 per cent of PSP, and an almost pure red color denoted 20 per cent or more. In the final cases, therefore, both the color and amount of PSP in the urine were recorded. Results much lower than 5 per cent were termed equivocal (Israel and Freed). Such results could have been considered as positive reactions if Speck's original criteria were followed.

On occasion during the study, 10 per cent sodium hydroxide was applied to secretions released by incising the dilated blocked tube in the laboratory of pathology. In several instances, PSP solution was found trapped in the tube as evidenced by a deep red reaction. Another experiment involved the uterotubal injection of methylene blue solution in the totally excised uterus and tubes; this procedure confirmed one case of blocked tubes and one case of completely patent tubes.

Analysis of Results

Ten cases disclosed obviously patent tubes both in situ and in the excised specimens and resulted in positive PSP tests. In these tests, no tension or resistance was obvious in the uterotubal system, except for one case in which uterotubal injection of the excised specimen in the laboratory revealed complete patency. In this instance dye recovered in the urine was deep pink red and represented 14 per cent PSP.

Three cases with tubal patency gave a negative or equivocal test depending on the criteria used. One revealed an end point which was a very faint pinkish purple. Another was a patient with huge fibroids and 15 c.c. of the dye were injected with no tension. The color obtained was violet pink representing 2.4 per cent of the dye. The third case gave a fainter color which was determined to represent 0.8 per cent of the dye in the urine specimen. No resistance or tendency to reflux was apparent in any of these cases.

Two cases represented situations in which patency was present in one tube while the other tube was unequivocally closed. These situations resulted in positive PSP tests. The first of these was a case of marked bilateral salpingitis isthmica nodosa; one of the tubes was patent at the fimbriated end, and, despite advanced pathologic involvement, this case is listed as one of patent tubes. The second patient had a large tuboovarian cyst on one side and a definitely patent, uninvolved tube on the other side. The patency of the normal tube was confirmed in situ by injecting saline. In both cases, resistance to injection and reflux were evident. In the second case resistance in the uterotubal system was so great that only 7 c.c. could be injected and 4 c.c. were recovered at the end of the test.

Two cases were determined to have blocked tubes and gave definite negative tests with no discernable discoloration of the alkalinized urine. The first was a patient with bilateral hydrosalpinx follicularis. Resistance to injection and reflux were present. The second was one of chronic salpingitis and perisalpingitis with blockage of the distal ends of the tubes. In this case, there was no apparent resistance to a 10-c.c. injection of PSP solution. However, 9 c.c. of the solution were recovered at the end of the test. This represents the only case in the series of blocked tubes in which injection resistance was not found.

Three cases represented closed tubes in which the test resulted in a color reaction which was very faint pinkish violet. Color, however, was definite and if Speck's criteria were used, these must be considered positive tests. On the other hand, Israel and Freed would consider this group as equivocal or possibly negative. The first was one of bilateral hydrosalpinx. The second instance represented a patient with only a uterus and one ovary remaining fol-

lowing multiple operations; 7 c.c. of PSP solution were injected and 5 c.c. recovered. The third, a patient with left hydrosalpinx and previous right salpingo-oophorectomy, gave a faint color reaction which represented less than 1 per cent of dye.

The remaining 5 cases represented blocked uterotubal systems in which the PSP tubal patency test resulted in positive test colors. The first was a patient with multiple fibroids and bilateral hydrosalpinx follicularis. One of the tubes in this patient contained trapped PSP solution as determined by applying alkali to the secretion which escaped forcefully when the tube was incised following its removal. The second was a patient with multiple fibroids and bilateral hematosalpinx. The third had a bilateral hematopyosalpinx. One tube and ovary were excised and a cornual resection performed on the less involved tube. Only 7 c.c. of solution could be injected and 5 c.c. were withdrawn at the end of the test. The fourth case was interesting in that this specimen (totally removed uterus and tubes) was vigorously injected with methylene blue solution in the laboratory without any material appearing through the distal ends of the tubes. The tubal patency test in this patient was positive and injection tension was obvious during the test since only 7 c.c. of solution could be injected. Grossly, the distal portion of one tube in this specimen appeared open, but the uterotubal injection in the excised specimen proved the lack of full patency. The last patient was injected with 7 c.c. of solution and gave a positive test in the presence of bilateral grossly dilated blocked tubes. Reflux which occurred spontaneously amounted to 5 c.c. The standards of Israel and Freed in this case gave a 4 per cent content of PSP in the alkalized urine specimen which turned a light pink.

Comment

Usage will quickly define the limitations of a new test. Any test for tubal patency should at least approach the Rubin Test and uterosalpingography in accuracy. In this small series of surgically confirmed cases, the PSP tubal patency test gave many irregular results.

Ten of the twenty-five cases presented blocked uterotubal systems and gave a variety of results when the PSP tubal-patency test was applied (Table I).

TABLE I. RESULTS OF PSP TUBAL PATENCY TEST IN 10 PATIENTS WITH BILATERAL NONPATENT TUBES

Negative tests (no color)	2
*Equivocal tests (very faint pink)	3
Positive tests (pink or red)	5

*Standards of Israel and Freed.²

Fifteen of the twenty-five cases presented patent uterotubal systems (including two cases with only one patent tube) and also gave inconsistent results (Table II).

TABLE II. RESULTS OF PSP TUBAL PATENCY TEST IN 15 PATIENTS WITH PATENT TUBE OR TUBES

Positive tests (pink or red)	12
*Equivocal tests (very faint pink)	3

*Standards of Israel and Freed.²

In the blocked uterotubal system, the dilated and diseased tube may, in some cases, possess the ability to absorb PSP solution in variable amounts. Injection pressure may be a factor in absorption of the material, but this pressure is unavoidable where nonpatent tubes are encountered.

In twelve of the twenty-five cases cited, there was either unilateral or bilateral tubal obstruction and in each of these cases, except one, resistance to injection of the solution was evident. Reflux, either spontaneously, or by drawing back on the syringe, was also evident in many of these instances. We feel that the increased pressure necessary for injection, and reflux phenomena, as well as the appearance of the gross specimens, are good clinical signs for diagnosis of tubal blockage.

The color end point of the PSP tubal patency test, as originally outlined, can be confusing. For example, there was a total of six equivocal tests (very faint color). Three of these tests represented open tubal systems and three, closed systems. Only by gross examination of these specimens could it be definitely determined which tubes were completely patent or blocked.

Summary and Conclusions

1. Twenty-five patients were subjected to the PSP tubal patency (Speck) test. In each case, the condition of the pelvic organs was determined in the excised specimen.

2. Only 14 tests (2 negative and 12 positive) were correctly correlated to the actual condition of the tubes.

3. Five tests represented false positive reactions. (Definite color reaction in presence of blocked tubes.)

4. There were six equivocal (very faint color) tests, 3 in the presence of open tubes and 3 in the presence of closed tubes.

5. The PSP tubal patency test has limited usage because of the indefinite color end points as well as the ability of some dilated, blocked, and diseased tubes to absorb the testing material (PSP solution).

The helpful suggestions of Drs. A. First and S. L. Israel of the Department of Gynecology are appreciated. We wish, also, to thank the members of the Department of Pathology, under the supervision of Dr. D. Meranze, for their studies of the pathologic specimens.

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THE MANAGEMENT OF THREATENED ABORTION: A STUDY OF 100 CASES

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THE proper management of threatened abortion is a very controversial problem, one on which there is little agreement. Many different drugs have been proposed, each with its enthusiastic adherents, and each with reputed amazing ability to salvage the threatened loss of the pregnancy. Currently, on the basis of reports by the Smiths of Boston, stilbestrol in very large doses is the drug of choice. In an attempt to evaluate the efficacy of this drug in the management of threatened abortion, a controlled study of 100 cases was undertaken by the authors.

To clarify and limit discussion, the terms abortion and threatened abortion should be clearly defined. Abortion refers to the detachment or expulsion of the ovum of less than twenty weeks' gestation. Threatened abortion is defined as the occurrence of uterine bleeding with or without uterine cramps in a uterine pregnancy of less than twenty weeks' gestation.

The incidence of spontaneous abortions was estimated by Hertig¹ at 10 per cent of all pregnancies and threatened abortions at 16 per cent of all pregnancies. Other authors^{2, 3, 4} estimate the incidence of threatened abortion at 18 to 20 per cent. One in every six pregnancies, then, threatens to abort, a figure which emphasizes the importance of this complication.

Hertig has also shown that 70 per cent of abortions are the result of developmental defects in the ovum or its appendages, and that another 17 per cent are due to unavoidable maternal causes. Thus, in only 13 per cent of abortions may the outcome be altered by therapy. Some authors believe that bed rest and sedation alone will salvage as many pregnancies as any therapeutic regime, others believe that progesterone will materially increase the salvage rate, while others believe that diethylstilbestrol therapy will give the best results.

Methods and Materials

This series of cases is made up of 136 patients who were admitted to the dependents' service at the U. S. Naval Hospital, Long Beach, Calif., with diagnoses of threatened abortion. In 36 cases the diagnosis was later proved to be in error, leaving 100 cases of threatened abortion. Each of these patients had the signs and symptoms of pregnancy, had missed one or more menstrual periods, had uterine bleeding with or without uterine cramping at the time of admission, an undilated cervix and a normal temperature, and had passed no portion of the products of conception per vaginam.

*The opinions expressed here are those of the authors and do not necessarily reflect those of the Navy Department.

As soon as the diagnosis had been made, the patient was admitted to the hospital and placed on one of two treatment routines in order of admission: the first patient Routine I, the second patient Routine II, the third patient Routine I, etc. The routines used were as follows:

- I. a. Bed rest until asymptomatic for 24 hours.
b. Phenobarbital, 0.1 Gm. three times daily until asymptomatic for 24 hours.
c. Demerol 100 mg. on admission and 50 mg. every 4 hours until cramping had ceased. Pantopon was later substituted for Demerol, due to the high incidence of nausea and vomiting with the latter.
- II. a. Bed rest and sedation as in Routine I.
b. Diethylstilbestrol 25 mg. every 30 minutes for 6 doses, then 100 mg. daily until asymptomatic for 24 hours, then 50 mg. daily to the twenty-eighth week of pregnancy.

The only exceptions made were in the cases of patients who were readmitted. These patients were reassigned their original routines. Only nine patients were admitted as having a threatened abortion more than once. Thirty-seven patients were treated on Routine I and 63 on Routine II.

In all cases where there was any question as to the correct diagnosis, a serum Friedman test was done. Patients who were discharged from the hospital as still pregnant were re-examined four weeks later in the outpatient department, to verify the diagnosis. In doubtful cases another Friedman test was done.

TABLE I. RESULTS OF TREATMENT

ROUTINE	NO. OF CASES	RETAINED TO VIABILITY	ABORTED
I	37	21 (57%)	16 (43%)
II	63	32 (51%)	31 (49%)

Results

One hundred thirty-six cases were treated according to one of the routines outlined. Thirty-six were incorrectly diagnosed and were eliminated from consideration. In Table I are shown the results in the remaining 100 cases. On Routine I 57 per cent retained their pregnancies; on Routine II 51 per cent retained their pregnancies. Each of these patients maintained her pregnancy to viability.

Twenty-eight patients were given progesterone orally (30 mg. per day), in addition to stilbestrol, during their hospitalization. Twelve of these patients successfully continued their pregnancies to viability. The dosage of progesterone was so low and continued for such a short time that the effect of this drug could have been only negligible. These patients were therefore included with those who received stilbestrol alone.

TABLE II. ERRORS IN DIAGNOSIS

Ectopic pregnancy	1
Inevitable abortion	12
Not pregnant (Hospital diagnosis)	13
Not pregnant (Clinic diagnosis)	10
Total errors in diagnosis	36 (24%)

Table II is a compilation of the final diagnoses in the 36 cases incorrectly diagnosed. Twelve patients were admitted as having threatened abortions, which were actually inevitable or incomplete on admission. This group was given the benefit of treatment until the diagnosis was established. Thirteen patients admitted as having threatened abortions were proved by subsequent

examination and Friedman tests during the course of hospitalization to be not pregnant. Of more significance is a group of ten patients who were discharged from the hospital as still pregnant, but who on examination in the prenatal clinic four weeks later were found to be not pregnant. This group will be discussed further.

Discussion

Most of the recent articles in the literature recommend the use of either progesterone or stilbestrol in the treatment of threatened abortion. The use of the former is based on studies which showed that progesterone inhibits uterine contractions and that it is somehow essential to the maintenance of the pregnancy.

During the first three months of pregnancy progesterone is secreted by the corpus luteum. On about the seventieth day the syncytium of the chorionic villi begin to take over the secretion of progesterone, and the corpus luteum degenerates. Most abortions occur at about this time. Theoretically, the administration of progesterone to a patient threatening to abort will increase the amount of available progesterone during this critical period of change-over from corpus luteum to placenta and will inhibit uterine contractions, thus helping to maintain the pregnancy.

The progesterone level in a given patient is not measured directly. Instead, the amount of sodium pregnandiol glucuronate excreted in the urine is determined. The latter probably represents the excretion product of progesterone and indicates the amount of available progesterone present. Davis and Fugo⁵ showed that the pregnant patient in metabolizing progesterone had a return of 30 to 35 per cent as pregnandiol in the urine. In most pregnancies which threaten to abort, the levels of pregnandiol are normal, indicating no lack of progesterone. Guterman and Tulskey⁶ studied pregnandiol levels in 335 threatened abortions and found them normal in 57 per cent. Approximately 80 per cent of these patients retained their pregnancies whether they were or were not treated with progesterone. Forty-three per cent of the 335 patients had low pregnandiol levels. Ninety-seven per cent of these aborted in spite of progesterone therapy which varied from 1 to 25 mg. per day. These authors concluded that this dosage level was entirely inadequate in those cases in which the pregnandiol level was low and recommended dosages of 80 to 120 mg. intramuscularly per day. In a very small series (9 cases), treated in this manner they report a salvage rate of 45 per cent. We have no figures to prove or disprove the value of progesterone in management of threatened abortion.

The use of diethylstilbestrol in the treatment of threatened abortion is based on the investigations of Smith, Smith, and Schiller.⁷ They state that stilbestrol causes increased production of progesterone during pregnancy, probably by the placental syncytium, as a result of increased utilization of chorionic gonadotropin. It should be emphasized that according to those authors the value of stilbestrol in preventing abortion is by increasing the amount of available progesterone, and not by increasing the amount of estrogenic substances present.

In 1948 Smith⁸ reported 219 cases of threatened abortion treated by a group of 117 contributing obstetricians who employed the stilbestrol-treatment regime outlined by these authors. Seventy-eight per cent of these patients maintained their pregnancies to 28 weeks and 72 per cent obtained living children. It should be noted that there were no controls reported in this series: the results were merely compared to Hertig's figure of a spontaneous cure rate of 50 per cent.

Rosenblum and Melinkoff⁹ treated 81 cases of threatened abortion with large doses of stilbestrol. They reported 86 per cent of these cases as successfully continuing the pregnancy.

According to the Smiths, the mechanism through which stilbestrol prevents abortion is the stimulation of increased production of progesterone. We should be able to demonstrate elevated pregnandiol levels in the urine of patients receiving stilbestrol. That such is not the case was shown by Davis and Fugo⁵ who administered large amounts of stilbestrol daily to 15 pregnant patients during the first 16 weeks of gestation. They found no alteration in the normal levels of pregnandiol excretion. In a personal communication, Hanley¹⁰ reports he carried out a similar study with 70 pregnant patients, 35 with stilbestrol and 35 without stilbestrol, and he failed to demonstrate any alteration in the normal levels of pregnandiol.

If stilbestrol does not stimulate the increased production of progesterone, its use in threatened abortion has no theoretical basis. The results of our study indicate that stilbestrol did not increase the number of pregnancies salvaged. We have therefore concluded that stilbestrol is of no value in the treatment of threatened abortion.

The diagnosis of pregnancy at six to eight weeks is not always a simple matter. In this series ten patients were admitted as threatened with abortion, placed on one of the routines of treatment, and discharged from the hospital as still pregnant, but on re-examination in the outpatient clinic were found to be not pregnant. Nine of the ten so treated had been receiving stilbestrol, and one had been receiving no therapy. The prolonged administration of stilbestrol to the nonpregnant patient may prolong the amenorrhea and produce breast changes, thus continuing the impression that the patient is pregnant. Only prolonged observation and repeated Friedman tests clarify the picture. Two of these patients were eventually curetted for continuous vaginal bleeding; the pathologic diagnosis in these cases was "endometrial hyperplasia," probably the direct result of the prolonged stilbestrol therapy.

Summary

1. A study of the therapy of 100 cases of threatened abortion is presented, treated by one of two routines of therapy: I. Bed rest and sedation, II. Bed rest, sedation and stilbestrol.

2. The study indicates that stilbestrol therapy, in large doses, results in no increase in salvage rate of threatened abortion over bed rest and sedation alone.

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ELECTIVE INDUCTION OF LABOR*

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THIS subject is presented with complete awareness of its controversial nature. Elective induction of labor probably reached its greatest popularity during the years 1942 to 1946, when many obstetricians were carrying extremely heavy loads. It is recognized that many outstanding obstetricians regard this procedure as "meddlesome obstetrics."

It is felt that there have been several significant advances in obstetrics in the last decade and that there will be wide acceptance of this procedure in the next decade. The objections to this procedure are that it carries an added risk for both the mother and the baby. It is my intention to present evidence which, in my experience, indicates that induced labor in *properly selected* cases is no different from spontaneous onset. Greenhill¹ has stated, "Elective induction of labor, when performed at the *proper* time by one who knows how, carries no risk." Grier² reported in 1947 a series of 123 cases of elective induction and stated, "The precipitation of imminent labor is a justifiable procedure."

The question may be asked, "What are the reasons for elective induction of labor?" It is believed that it offers the patient considerable relief from anxiety and apprehension, especially those who live long distances from the hospital and those with histories of short labors. Is it not just as reasonable to relieve a pregnant woman's mental suffering as it is to relieve her physical pain during labor? Is there anyone who believes that the drugs and anesthetic agents used during labor carry no risk for the mother and her baby?

The material presented here consists of a comparison of data gathered from 100 patients who had elective induction of labor and 100 whose labor started spontaneously. The 100 control cases were not chosen at random, but were selected as cases considered to be normal prior to the onset of labor. No cases of premature birth occurred in either series. Every attempt was made to make the comparison as fair as possible.

The criteria for selecting the cases for induction were as follows:

1. There must be no cephalopelvic disproportion.
2. The pregnancy must be at or near term.
3. The vertex, preferably, should be presenting.
4. The head must not be floating or ballotable.
5. The cervix must be thin, soft, and open at least 1 cm. According to Grier² the onset of labor should be imminent and the obstetric prognosis good. No patients were in the induced group without their consent and full knowledge of the procedure contemplated. There were 47 primiparas in the induced group and 59 in the spontaneous group.

*Read before the Texas Association of Obstetricians and Gynecologists at the Annual Meeting, Feb. 3, 1950, San Antonio, Texas.

Mechanical rupture of the membranes was the method used. In addition, 49 patients received Pitocin to initiate uterine contractions. Following their admission to the hospital, the patients were prepared in the usual manner and then draped for pelvic examination. Under careful aseptic technique, rupture of the amniotic sac was carried out. Pitocin was administered subcutaneously in minim doses usually after a period of 1 to 2 hours if labor had not already begun. The type of delivery and the amount of Pitocin used are shown in Table I.

TABLE I. TYPE OF DELIVERY

DELIVERY			PITOCIN		
	INDUCED	SPONTANEOUS	AMT. (MINIMS)	USED	NOT USED
Forceps:				49	51
Low	82	78			
Mid	3	2			
Spontaneous	13	18	4	40	
Breech	2	2	4-5.5	8	
Episiotomy	92	93	5 5+	1	

Fifty-one per cent of the patients received no Pitocin at all. Several of the remaining 49 per cent received only $\frac{1}{2}$ minim and many had only one or two minims. Forty-eight of the patients received $5\frac{1}{2}$ minims or less. One patient had a desultory labor with a definite uterine inertia and received 19 minims in doses of 1 and 2 minims at intervals of 30 minutes to 2 hours. All Pitocin was given with a tuberculin syringe. A comparison of the types of delivery in the two groups revealed no significant differences. Ninety-two patients of the induced group and 93 of the spontaneous group had episiotomies done. Piper forceps were applied to the aftercoming head in all four of the breech cases. One patient with breech presentation in the induced group was in labor less than 3 hours and the other one less than 10 hours. In each instance the presenting part was well down in the pelvis.

The latent period is defined as the time interval elapsing between the rupture of the membranes and the onset of actual labor. Latent periods of the induced group and a comparison of the maximum temperatures of both groups are shown in Table II.

TABLE II. TEMPERATURE RECORD

MAXIMUM TEMPERATURE			LATENT PERIODS		
	INDUCED	SPONTANEOUS			
-99° F.	61	49	0	42	
99.2°-100° F.	34	40	1-3	34	91%
100.2°-101° F.	4	4	3-6	15	less
101.2°+ F.	1	3	6-12	5	than
			12-12.5	4	6 hrs.

Determination of the exact time of onset of labor is impossible; therefore, all patients who were in active labor in less than one hour are listed as having no latent period. Forty-two patients fell in this group. Thirty-four patients had latent periods from 1 to 3 hours. Fifteen patients had latent periods from 3 to 6 hours. Five patients had latent periods from 6 to 12 hours. Four patients had latent periods of 12 to $12\frac{1}{2}$ hours. Ninety-one per cent had latent periods less than 6 hours.

Sixty-one per cent had maximum temperatures of 99° F. or less in the induced group as compared to 49 per cent in the spontaneous group. Thirty-four per cent in the induced group had maximum temperatures from 99.2° to 100° F. as compared to 40 per cent in the control group. Four per cent in each

group had maximum temperatures of 100.2° to 101° F. One per cent in the induced group and 3 per cent in the controls had maximum temperatures above 101.2° F. Actual morbidity, considered to be temperatures above 100.4° in two consecutive 24-hour periods, occurred in 1 case in the induced group and in 5 cases (5 per cent) in the control or spontaneous group. All 6 of the morbid patients were primiparas. The 1 patient of the induced group had no Pitocin, low-forceps delivery with episiotomy, maximum temperature of 101° F., zero latent period, and labor of 4 hours, 7 minutes. Of the morbidity cases in the spontaneous group, the length of labor varied from 6 hours, 15 minutes to 23 hours, 32 minutes (4 were less than 11 hours). Each of the 5 patients was delivered by low forceps and episiotomy. Disruption of the episiotomy did not occur once in the 200 cases nor was there any apparent infection of the wounds.

TABLE III. LENGTH OF LABOR

	0-2 HOURS	2-4 HOURS	4-6 HOURS	6-10 HOURS	10-20 HOURS	20+ HOURS	SHORTEST	LONGEST
<i>Induced.</i> —								
Primiparas	2	11	17	14	2	1	1 hr. 37 min.	21 hrs. 59 min.
Multiparas	18	20	12	2	1	0	55 min.	12 hrs. 20 min.
<i>Spontaneous.</i> —								
Primiparas	0	12	15	16	14	2	2 hrs. 15 min.	23 hrs. 32 min.
Multiparas	7	9	17	6	2	0	1 hr. 12 min.	12 hrs. 17 min.
	Labor less than 10 hours					Induced 96%	Spontaneous 82%	

Determination of the time of actual onset of labor in the spontaneous group is impossible; therefore, each patient who was admitted to the hospital in active labor was considered to have started one hour before. No claim is made for the complete accuracy of the length of labors in the spontaneous group, but the error is consistent and therefore is considered to be significant. The error would tend to shorten the actual length of labor which would make them compare more closely to the induced group. Twenty per cent of the induced group had labors less than 2 hours and there were 7 per cent in the control group. Thirty-one per cent of the induced group and 21 per cent of the controls had labors from 2 to 4 hours' duration. Twenty-nine per cent of the former and 32 per cent of the latter had labors from 4 to 6 hours. Eighty per cent of the induced group had labors of 6 hours or less as compared to 60 per cent in the spontaneous group. As expected, the multiparas' labors in each group were much shorter than that of the primiparas. The longest labor in either group was in a primipara in the control group, 23 hours 32 minutes. The shortest labor in either group was in a multipara in the induced group which lasted 55 minutes.

Summary

In this series, the length of labor of the induced group was shorter than of the control group. The maximum temperatures and the morbidity rate were higher in the spontaneous group than in the induced group. There were no stillborn infants or neonatal deaths in either group, and there were no maternal deaths. The morbidity rate was no higher than the average reported from other hospitals. There were no abdominal deliveries in either group.

Conclusions

1. Elective induction of labor carries no added risk if done at the proper time.

2. The "ripeness" of the cervix is the one most important factor in the selection of cases.

3. There was no appreciable difference in the course of labor in the two groups.

4. The majority of patients prefer this procedure and will readily accept it when given the opportunity.

5. Pitocin in small doses is a safe and effective drug.

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THE SALMON MODIFICATION OF THE OVARIAN HYPEREMIA REACTION IN 1,042 CONSECUTIVE PREGNANCY TESTS*

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FOLLOWING the development of the Aschheim-Zondek and Friedman tests, Eberson and Silverburg¹ in 1931 described the use of female immature rats for pregnancy tests which required only 36 to 48 hours. Frank and German² in 1941 reduced the time for a test to 24 hours. Aschheim³ in 1942 described a modification of the original Aschheim-Zondek test with both vaginal smears and ovarian-follicle formation as diagnostic criteria; results were available in 72 hours.

Salmon and associates⁴ in 1942 reported that hyperemia uniformly was detectable in the immature rat ovary 6 hours after the injection of pregnancy urine, and that in some instances the hyperemia was more striking at 6, than at 12 or 24 hours. The reaction was related to the gonadotropins of pregnancy urine, since a similar reaction was produced with purified chorionic gonadotropin but did not occur with urines in which the gonadotropin had been inactivated by boiling. In 1943⁵ the same group reported 96.3 per cent accuracy in pregnancy diagnosis with 2-hour tests and 98 per cent accuracy with 6-hour tests. This study analyzes results of 1,042 consecutive tests on 980 patients, done in the laboratory of the Division of Endocrinology.

Method

Each of three immature female rats, 21 to 25 days of age and weighing 35 to 55 grams, of the Vanderbilt strain, are injected subcutaneously with 2 c.c. of a morning urine specimen. The urine is not used when the specific gravity is less than 1.014. Three rats are used because occasionally ovaries are refractory. The rats are killed with ether after 6 hours and the ovaries are examined immediately. Positive reaction is indicated by macroscopic ovarian hyperemia in at least two of the six ovaries. A negative test is characterized by pale, pink, or blanched ovaries.

Results

The results in Table I compare the data of ovarian hyperemia reaction with the established diagnosis. The patients of this study ranged from 13 to 52 years of age. The tests were done at diverse times, which ranged from 5 days after the first missed menstruation to 2 weeks ante partum.

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TABLE I. RESULTS OF 1,042 SALMON TESTS ON 980 PATIENTS

CLINICAL DIAGNOSIS	SALMON TEST	
	POSITIVE	NEGATIVE
Normal pregnancy	359	7
Nonpregnant	3	462
Threatening abortion	63	1
Incomplete abortion	36	14
Ectopic pregnancy	19	5
Missed abortion	0	9
Fibromyomatous uterus	0	53
Hydatidiform mole	6	0
Chorionepithelioma	5	0

Normal Pregnancy.—Positive tests were obtained 359 times and negative tests 7 times. Five patients supplied the 7 false negative tests. The menstrual periods of one of these patients had been irregular since menarche, with frequent episodes of no bleeding for 6 to 8 months. Two negative tests were obtained during the absence of bleeding for 8 months. A third test, done one month later, when there was roentgenologic evidence of a four and one-half months' pregnancy, was positive. Accordingly, there was a three and one-half months' pregnancy when the 2 negative tests were obtained. Another patient supplied one negative test despite a three and one-half months' pregnancy. Another pregnant patient yielded 2 negative tests approximately 2 months following cessation of flowing. Two other pregnant patients, respectively, had 3 tests each within 5-day intervals; 2 were positive and 1 was negative.

Nonpregnant Patients.—Negative tests were obtained 462 times and positive ones 3 times. One of the patients yielding a false positive test gave 2 negative tests, two and three days later. Another patient who gave a false positive test when she was 6 days "overdue" yielded a negative test one month later, despite the fact that she had not had a menstrual period. Another patient gave a positive test when 8 days "overdue" but a negative test one month later, following a normal menstrual period.

Patients With Threatening Abortions.—Sixty-three positive and 1 negative tests were obtained on patients with threatening abortions who subsequently aborted. The patient giving the one negative test 3 days later yielded a positive test.

Patients With Incomplete Abortions.—Thirty-six positive and 14 negative tests were secured. Histories revealed that 10 of the 14 patients with negative tests had aborted 14 or more days before the tests were done. The histories of the remaining 4 indicated they had aborted 3 to 8 days before the tests.

Patients With Ectopic Pregnancies.—Nineteen positive and 5 negative tests were obtained. Operative findings of the 4 patients giving negative tests indicated tubal abortion and the history suggested that this had occurred 10 or more days prior to the test. Another patient gave 3 positive tests, 13, 14, and 15 days before her negative test and her history indicated that tubal abortion occurred 12 days before the negative test.

Patients With Missed Abortions.—Nine negative results were obtained.

Patients With Fibromyomas.—Fifty-three negative tests resulted.

Patients With Hydatidiform Moles.—Six positive results were obtained.

Patients With Chorionepitheliomas.—Five positive results were obtained.

Comparison of Salmon and Friedman Tests.—Table II summarizes this comparison. Sixty-two simultaneous tests were done on 61 patients. Twenty-two pregnant patients gave positive tests by the Salmon method, whereas

20 positive and 2 negative results were obtained by the Friedman method. Thirty negative and 1 positive tests were obtained by the Salmon method on nonpregnant women whereas the Friedman method yielded 29 negative and 2 positive tests. Both methods gave positive tests on 2 patients with threatening abortions. Four patients with incomplete abortions gave positive Salmon tests and 3 positive and 1 negative Friedman tests. Two patients with ectopic pregnancies gave positive tests by both methods. A patient with a fibromyoma gave negative tests by both methods.

TABLE II. COMPARISON OF SALMON AND FRIEDMAN TESTS ON 61 PATIENTS

CLINICAL DIAGNOSIS	SALMON TEST		FRIEDMAN TEST	
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
Normal pregnancy	22	0	20	2
Nonpregnant	1	30	2	29
Threatening abortion	2	0	2	0
Incomplete abortion	4	0	3	1
Ectopic pregnancy	2	0	2	0
Fibromyomatous uterus	0	1	0	1

Comparison of Salmon and Aschheim-Zondek Methods.—Table III summarizes these comparisons. Thirty-two tests by each method were performed on 31 patients. All results agreed. Fifteen pregnant patients gave positive tests, 13 nonpregnant patients negative tests, 1 patient with threatening abortion a positive test, 2 patients with incomplete abortions positive tests, and 1 patient with ectopic pregnancy gave a positive test.

TABLE III. COMPARISON OF SALMON AND ASCHHEIM-ZONDEK TESTS ON 31 PATIENTS

CLINICAL DIAGNOSIS	SALMON TEST		ASCHHEIM-ZONDEK TEST	
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
Normal pregnancy	15	0	15	0
Nonpregnant	0	13	0	13
Threatening abortion	1	0	1	0
Incomplete abortion	2	0	2	0
Ectopic pregnancy	1	0	1	0

Comment

If the 14 negative tests in incomplete abortion and 5 negative results in tubal abortion are considered accurate, then the accuracy for 1,042 tests, of which 11 were wrong, is 98.94 per cent.

Four of the requisites of any laboratory test are: simplicity, rapidity, accuracy, and convenience. The Salmon test has fulfilled all of these requirements. Added to the convenience of an easily readable end point, the test has the advantage of economy over the Friedman and Aschheim-Zondek tests. Furthermore, toxicity of the urine to the test animal is minimal.

Albert⁶ has described the Salmon method as more accurate than other methods in predicting the outcome of the pregnancy. We have not found this true.

Farris⁷ reported false positive tests on climacteric women. We had no false positive tests on 34 women, aged 40 to 52 years. We had no false positive tests during the mid-interval of the cycle, or during menstrual periods, contrary to Farris' experience. His results, however, were based on a 2-hour rat

test which has been reported 95.5 plus per cent accurate by Kupperman and Greenblatt⁸ and as 96.8 per cent accurate by Fried.⁹ Our accuracy of 98.94 per cent suggests the advantage of 6-hour tests over 2-hour tests. Zondek and Sulman¹⁰ have reported an accuracy of 99 per cent or better for a 24-hour test.

Comparison of the Salmon and the Friedman methods indicates a slight superiority of the former over the latter. Comparison of the Aschheim-Zondek and Salmon methods reveals no differences in accuracy.

Summary

One thousand forty-two pregnancy tests on 980 patients using the immature rat ovarian hyperemia reaction described by Salmon are reported with an accuracy of 98.94 per cent. The test is practical because of its simplicity, rapidity, accuracy, and convenience.

The technical assistance of Ruth Weisner and Betty Henry in assembling these data and in performing many of these tests is acknowledged.

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DYSPAREUNIA DUE TO CHRONIC NONSPECIFIC URETHRITIS

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A REVIEW of the English literature reveals that only slight recognition is given to chronic urethritis as a cause of dyspareunia.¹⁻¹³ The purpose of this paper is to present twenty-three cases in which chronic nonspecific urethritis was the cause of dyspareunia and to emphasize the importance of excluding urethral disease as a cause of painful intercourse.

The search for the cause of dyspareunia in a given case must, of course, include a meticulous gynecological investigation. The presence of perineal scarring, vaginitis, parametritis, uterine malpositions, and adnexal pathology should be excluded. When such "local" causes cannot be found, the case is usually referred to a psychiatrist. In a significant number of cases, however, the presence of urethral disease may be suspected when a history of painful and frequent urination is obtained or by the eliciting of tenderness along the course of the urethra.

The exact cause of chronic nonspecific urethritis is not completely understood. Any condition which reduces the resistance of the urethral mucosa to disease may initiate the pathological changes which result in chronic urethritis. Over 95 per cent of patients with this disease are married, which fact suggests that trauma of intercourse is an etiological factor. The proximity of the urethra to the vagina and rectum facilitates transmission of organisms from these contaminated passages to the urethra.

The outstanding symptoms of chronic urethritis are bladder irritability and pain, the latter being either local or referred. Frequency, pain, burning, urgency of urination, and a sensation of pressure in the suprapubic region and/or a feeling of incomplete emptying of the bladder are the chief urinary symptoms. In previous publications, one of us (A. J. B.)^{1, 2, 14} has stressed the importance of chronic urethritis as a cause, not only of distressing urinary symptoms, but of vague lower abdominal pain and backache. Anatomically, the urethra is located in the erotic zone where sensory nerve endings are numerous and acutely sensitive to stimuli. It is logical to assume that pressure of the penis against an inflamed, tender, scarred urethra may be extremely painful.

One may obtain a history from the newly wed of a severe attack of so-called "cystitis" or "pyelitis," following which painful intercourse occurred. At times, the patient may have been married for a number of years before the onset of symptoms. Dyspareunia may vary from slight discomfort to pain so severe as to make coitus unbearable. The urine is significantly free of infec-

tion in the great majority of cases. The diagnosis of chronic urethritis is made by cystourethroscopic examination. The inflammatory changes are limited chiefly to the posterior third of the urethra, the bladder neck, and the trigone. Usually, the mucosa at the bladder neck is irregular and interrupted by small cysts or polyps. The trigone is also frequently covered by small cysts in conjunction with the picture of trigonitis.^{1, 2, 8, 9, 11, 14}

Treatment involves three simple procedures: (1) irrigation and distention of the bladder with a bland antiseptic solution; (2) dilatation of the urethra; (3) instillation of silver nitrate solution into the urethra.

Irrigation of the bladder alone will frequently relieve the patient of her symptoms. The urethra is actually dilated by the catheter; irrigation and overdistention of the bladder break the chain of reflexes by which the bladder and diseased urethra have been functioning. In many cases the lumen of the urethra has become smaller due to the presence of scar tissue. This contraction is overcome by dilating the urethra with sounds up to No. 26 or 28 French. Silver nitrate solution has a mildly astringent effect and thus serves to cauterize the sensitive nerve endings in the posterior urethra and in the base of the bladder. If the urethra is extremely tender, 0.25 per cent solution is used first and, with subsequent treatments, the strength of the solution is increased to 2 per cent. In some resistant cases, 10 per cent solution is applied directly to the posterior urethra through an endoscope. Rarely, the bladder neck must be cauterized using a high frequency current. There may be recurrence of symptoms. Usually one or two treatments will again afford complete relief.

Analysis of Cases

Seven hundred seventy women with chronic nonspecific urethritis were observed during a sixteen-month period from Jan. 1, 1947, to May 1, 1948. Of this group, twenty-three patients complained of dyspareunia as one of their symptoms. Gynecological and psychogenic factors were excluded as far as determinable. The intensity of dyspareunia was graded from one to four; Grade I being the least severe, and Grade IV being the most severe. The youngest patient was 21 years old, the oldest, 47, the average age being 31 years. The duration of symptoms before the patient sought medical treatment varied from three weeks to fifteen years, the average time being 2.5 years.

There were four patients with slight or Grade I dyspareunia; thirteen patients had Grade II (moderate) dyspareunia; three patients had Grade III (severe) dyspareunia; and three patients had Grade IV (very severe) dyspareunia. All patients were treated by the method which was outlined above.

The results of treatment are briefly summarized: Thirteen women obtained complete relief of symptoms; ten patients noted definite improvement in that intercourse was only occasionally painful or had become less painful. Of the patients with Grade I dyspareunia, three were completely relieved, one improved. Seven patients with Grade II dyspareunia were completely relieved, six were improved. Two patients with Grade III dyspareunia were completely relieved, and one improved. One patient with Grade IV dyspareunia was completely relieved, and two were improved (Table I).

One of the most satisfactory results obtained was in a 33-year-old nullipara, Mrs. G. S., who had been married for eight years. During the first five years of her marriage, intercourse had been completely satisfactory. Then she abruptly developed extremely frequent

and painful urination, often accompanied by urgency incontinence. Soon after this, intolerable dyspareunia developed. The urinary incontinence became so severe that she was forced to wear a sanitary pad. Examination revealed an excruciatingly tender urethra. Urinalysis was negative. Cystourethroscopic examination revealed marked posterior urethritis with numerous polyps around the bladder neck. The trigone was covered with multiple cysts. Following the first treatment, her symptoms were greatly relieved. Daily treatments were carried out, and within ten days all symptoms had disappeared completely. She was advised to refrain from intercourse for a period of one month. After this time, completely satisfactory sexual relations were resumed. She has been checked at regular intervals. The urethra is treated every three months, and she remains asymptomatic.

TABLE I. RESULT OF TREATMENT FOR DYSpareunia

DEGREE OF DYSpareunia	GRADE I	II	III	IV	TOTAL
Number of patients	4	13	3	3	23
Completely relieved	3	7	2	1	13
Improved	1	6	1	2	10

Summary

Chronic nonspecific urethritis is a relatively common condition in women. Dyspareunia was a prominent symptom in twenty-three of seven hundred seventy cases in which the only diagnosis was chronic urethritis.

Conservative treatment to the urethra consisting of bladder distention, urethral dilatation, and instillation of silver nitrate solution produced complete relief of dyspareunia in thirteen of the patients and definite improvement in ten. Chronic urethritis should be excluded as a cause of dyspareunia in each case in which a gynecological cause is not apparent.

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GRANULOMA INGUINALE OF THE CERVIX UTERI AND VULVA TREATED WITH STREPTOMYCIN

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WITH the introduction of new drugs in the therapy of granuloma inguinale, attention should be directed to the response to treatment of various anatomic sites of this disease so that a total evaluation of the drugs can be made.

This paper reports five cases of granuloma inguinale of the vulva and three cases of granuloma inguinale of the cervix uteri treated with streptomycin (Table I). The diagnosis was proved histologically in each instance by the demonstration of Donovan bodies in sections prepared with the Giemsa stain.

TABLE I. SUMMARY OF CASES

CASE NO.	PATIENT	RACE	AGE	SITE	DURATION OF DISEASE	DURATION OF STREPTOMYCIN THERAPY	TOTAL DOSE	LENGTH OF FOLLOW-UP	RESULT
1	Ju. W.	Negro	28	Cervix	1 mo.	5 days	20 Gm.	2 mo.	Cured
2	A. S.	Negro	37	Cervix	8 mo.	5 days	20 Gm.	3 mo.	Cured
3	F. T. N.	Negro	24	Cervix	2 mo.	5 days	20 Gm.	1 mo.	Cured (†)
4	M. L. W.	Negro	27	Vulva	7 yrs.	5 days	20 Gm.	10 mo.	Cured
5	B. K. G.	Negro	21	Vulva	3 mo.	5 days	20 Gm.	6 mo.	Cured
6	A. G.	Negro	23	Vulva	10 mo.	4 days	13 Gm.	10 mo.	Cured
7	M. T.	Negro	63	Vulva	11 mo.	6 days	40 Gm.	2½ mo.	Cured
8	Jo. W.	Negro	70	Vulva	5 mo.	6 days	24 Gm.	3 mo.	Cured

Granuloma Inguinale of the Vulva

Five cases are included in this category. All were Negro women whose ages ranged from 21 to 70 years. The duration of the disease varied from three months to seven years. Previous treatment included systemic antimony salts, local application of podophyllin in olive oil, boric acid, potassium permanganate, and surgical excision.

In each case the gross appearance of the vulval disease was consistent with the diagnosis of granuloma inguinale, which was established microscopically. The size of the lesions varied, ranging from bilateral labial lesions of 2.5 cm. in one patient to a lesion involving the entire vulva and anterior vaginal wall in another.

The 5 patients were hospitalized for streptomycin therapy after the diagnosis of granuloma inguinale was proved. They received streptomycin intramuscularly in divided doses over a four- to six-day period, the total amount ranging from 13 to 40 Gm. There was no clinical evidence of streptomycin toxicity.

Subjective improvement was apparent within forty-eight hours following the first injection of streptomycin and was best illustrated by a dramatic de-

crease in pain. Objective evidence of healing was not clear-cut until the fifth or sixth day following the institution of therapy. Healing, once in progress, continued until complete resolution occurred.

The patients have been observed for two and one-half to ten months following treatment. There have been no recurrences.

Two of the patients became pregnant after treatment. One of them (A. G.) had previously given birth to a viable child in the presence of active granuloma inguinale of the vulva. At that time she suffered a second-degree laceration of the perineum which extended through the lesion. A repair of the laceration was attempted but the wound did not heal. Following this and prior to streptomycin treatment intercourse was impossible because of pain. After streptomycin therapy and complete healing this patient became pregnant again and had a normal vaginal delivery without laceration of the healed site. The second patient (M. L. W.) was delivered by cesarean section because it was believed that the healed, scarred, fibrotic, narrowed anterior vaginal vault would be badly lacerated if vaginal delivery were permitted.

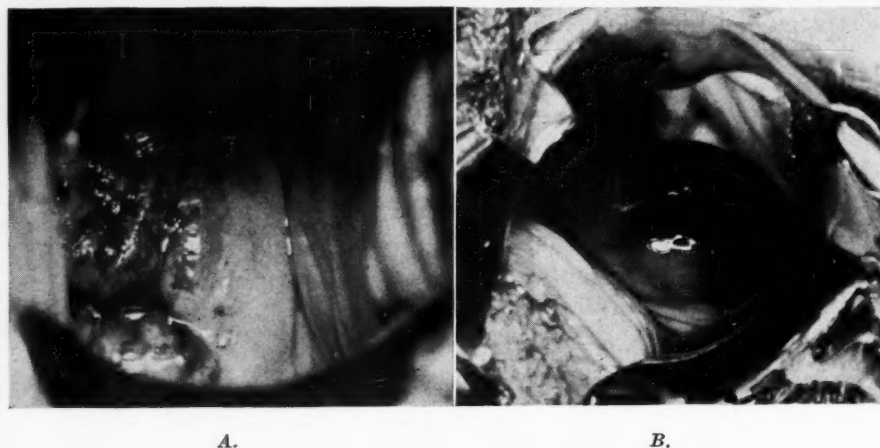


Fig. 1 (Case 3).—A, Granuloma inguinale of the cervix, before treatment. B, Three weeks following streptomycin treatment.

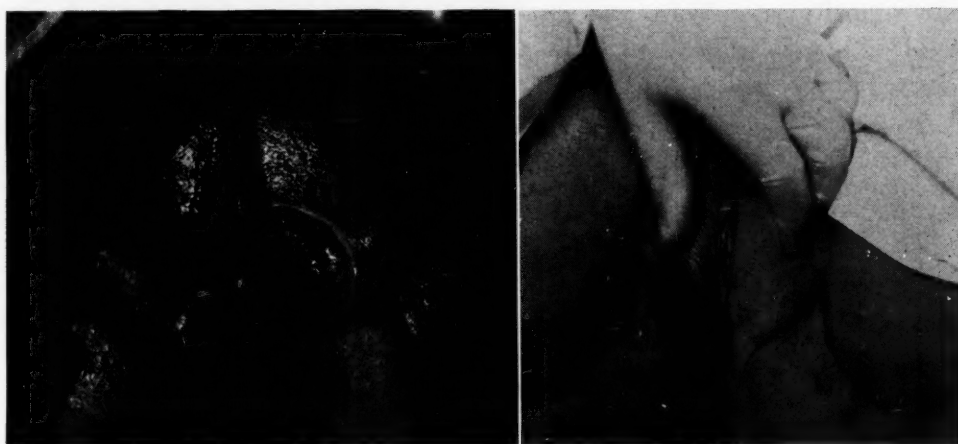
Granuloma Inguinale of the Cervix

Three cases are included in this group. All were Negro women whose ages were 24, 28, and 37 years. The duration of the disease was from one to eight months. The chief gynecologic complaints were leucorrhea, metrorrhagia, menometrorrhagia, and dysmenorrhea.

The cervices were eroded, friable, hypertrophic, granulating, and bled easily. The preliminary clinical diagnosis in each patient was carcinoma. Repeated biopsy specimens stained with hematoxylin and eosin were reported as chronic cervicitis; however, when they were stained by the Giemsa technique, Donovan bodies were demonstrated in each instance.

The patients were hospitalized and each given 4 Gm. of streptomycin intramuscularly daily for five days. One of them (A. S.) also received penicillin for a concomitant gonorrheal infection. The penicillin probably did not alter the course of the cervical granuloma inguinale. Another patient in this group (F. T. N.) received 3 Gm. of aureomycin orally in the eighteen hours just prior to the institution of streptomycin.

Within two weeks the three patients were asymptomatic except for a slight watery vaginal discharge in the older patient (A. S.). In two cases the cervixes, although markedly improved, were still somewhat inflamed. In these two cases a chronic nonspecific cervicitis was believed to have been present prior to the granuloma inguinale infection. Conization was done for the residual cervicitis and it afforded an opportunity to examine a large part of the cervix for Donovan bodies. The pathologic report was chronic cervicitis. No Donovan bodies were found. The immediate postoperative courses were uneventful. In the third patient, healing of the cervical lesion was apparent immediately after streptomycin therapy. The original disease had resolved to a cauliflower-like tumor of the anterior lip with hyperemia of both lips. Two weeks later the tumor was smaller, epithelization was almost complete, and the hyperemia was less. One week later, when the patient was last seen, a small superficial ulcer of the anterior lip was the only abnormality.



A.

B.

Fig. 2 (Case 7).—A, Granuloma inguinale of the vulva prior to treatment. B, Twenty-six days following streptomycin treatment.

Summary

1. Five patients with granuloma inguinale of the vulva and three patients with granuloma inguinale of the cervix were treated with streptomycin. The diagnosis was proved histologically in each instance.

2. The vulval lesions were cured with streptomycin.

3. Streptomycin treatment of cervical granuloma inguinale resulted in disappearance of the Donovan bodies in two cases. A mild nonspecific chronic cervicitis persisted; this was managed by electrosurgical conization. In the third and most recent case the cervix was almost completely healed when last seen.

Department of Case Reports

New Instruments, Etc.

GRANULOSA-CELL TUMOR OF EXTRAOVARIAN ORIGIN TRANSFORMED INTO A RETROPERITONEAL SARCOMA

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ALTHOUGH the literature on granulosa-cell tumor of the ovary is abundant, that dealing with the primary extraovarian form of this neoplasm is very meager; we were able to find only four reports concerning it. A fifth case is reported in which the neoplasm presented itself as a pararenal tumor and terminated four and one-half years later as a malignant sarcomatous growth with widespread metastases.

E. R., a 12-year-old white girl, was first admitted to St. Vincent's Hospital in October, 1944, complaining of a painless mass in the left half of the abdomen. This had been present for an estimated period of five to seven years and had not undergone any change in size. A laparotomy was performed and the mass was found to be a large retroperitoneal tumor intimately attached to the left psoas muscle and resting on the kidney; it was removed without difficulty.

The specimen was a soft, oval, completely encapsulated mass which measured 15 by 9 by 8 cm. and weighed 940 grams. The capsule was for the most part smooth, gray, and fibrous. Penetrating the capsule and protruding above its surface were several soft, red-gray masses 0.4 to 2 cm. in diameter. On section the tumor was composed of soft, yellow-gray, glistening tissue. It was cystic except for a portion of the periphery at one pole, where it was solid. The cysts varied from 0.5 to 1 cm. in diameter and were filled with clear, sticky fluid. The intervening walls were thin and fibrous.

Microscopic examination showed the tumor to be very cellular. The cells were of two types: one type loosely arranged, dark staining, oval or stellate, with round, vesicular nucleus and very scant eosinophilic cytoplasm; the other type uniformly oval and smaller, with dark-staining nucleus and imperceptible cytoplasm. These latter cells were compactly arranged, particularly about blood vessels. A very characteristic feature of the tumor was the presence of spaces of varying sizes and shapes, filled with a foamy, pink-staining material (Fig. 1). The spaces were lined by the first type of cell in a layer approximately six cells deep. At the base of this layer was another group of cells crowded together and oriented in a plane different from that of the cells of the first layer. Reticulum stains revealed the absence of silver fibrils in the loose surface layer and their presence in the more dense basal layer. The same silver-positive fibers were observed in the dense cellular areas about the blood vessels. Additional sections taken from the areas containing large cysts revealed atrophy of the lining cells and the presence of dense fibrous partitions between the cysts.

The diagnosis based upon microscopic examination was "granulosa-cell tumor of extra-ovarian origin."

Subsequent Course.—On March 21, 1949, the patient was readmitted to the hospital, complaining of pain in the neck and lower back. She stated that she had been well since her hospitalization approximately four and one-half years previously. However, in February, 1949, five weeks prior to this second admission, she developed a "head and chest cold"

followed by pain in the left lumbar region which persisted for a few days and then disappeared. In ten days pain recurred in the left lumbar region and radiated to the hip and down the posterior aspect of the left thigh. She had been admitted to another hospital where an x-ray picture of the chest was interpreted as negative and pictures of the spine disclosed lumbar scoliosis. After dismissal from the hospital she had been confined to her bed. The pain and stiffness spread to involve the entire back and neck. Menses were normal throughout.

Physical examination at this time showed a cooperative, chronically ill young girl showing evidence of recent weight loss. Findings were essentially negative except for nuchal rigidity and a few scattered râles at the lung bases. X-ray pictures of the chest showed diffuse and scattered areas of infiltration at the base of each lung. Red blood count was 4,310,000; white blood count 7,850; smear differential showed 66 per cent polymorphonuclear leucocytes, 34 per cent lymphocytes. The hematocrit was 43 mm. for the cell component. Urinalysis showed only one-plus albuminuria. The spinal fluid was normal. An electrocardiogram showed sinus tachycardia and right axis deviation.

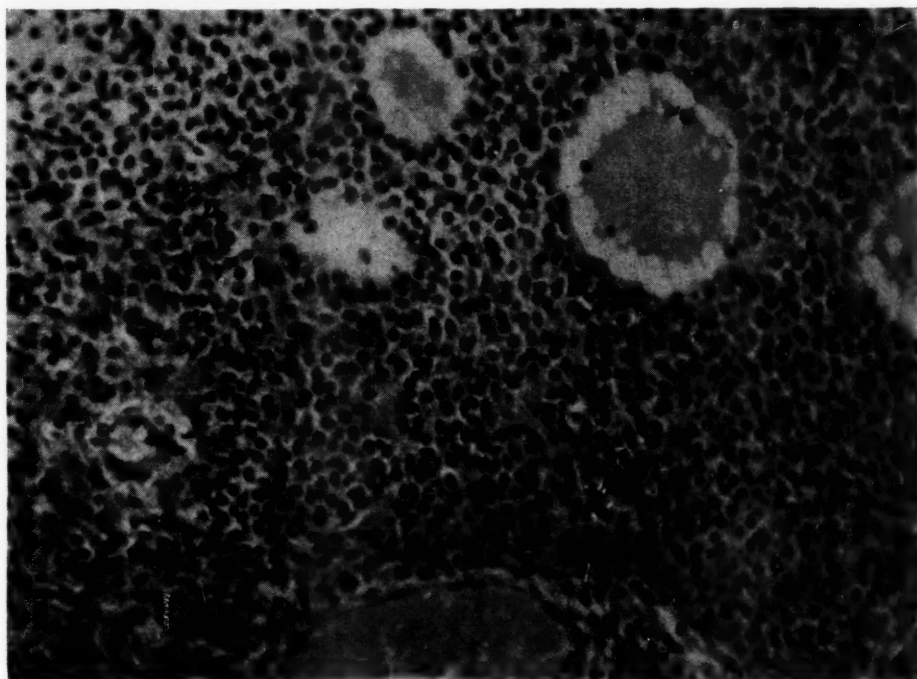


Fig. 1.—Section of tumor showing follicles of varying sizes. Note cellularity between follicles. (Low power; hematoxylin and eosin stain.)

During hospitalization the patient had intermittent fever which at times was as high as 103° F. On the sixth hospital day a pericardial friction rub was heard. X-ray pictures of the chest now revealed evidence of glandular enlargement in the mediastinum in addition to the parenchymal shadows noted previously; pictures of the cervical spine and pelvis were normal. Further studies included repeated blood cultures, which proved to be sterile. Agglutination studies for typhoid O and H, paratyphoid A and B, and *Proteus* X19 were negative. The carbon dioxide combining power of the blood was 36 volumes per cent. Cold agglutinins were positive in 1:4 dilution, negative in 1:8 dilution. Serum calcium was 12 mg. per cent; serum phosphorous 4.2 mg. per cent; serum bilirubin 0.8 mg. per cent; alkaline phosphatase 5.0 Bodansky units; Kahn test negative; urobilinogen positive in 1:10 dilution, negative in 1:20 dilution.

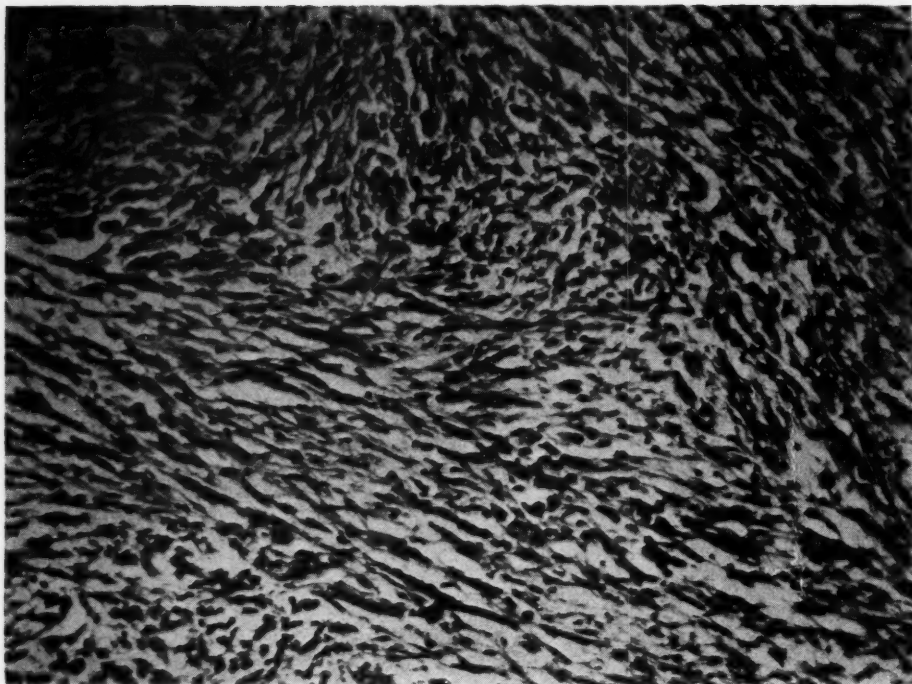


Fig. 2.—Microscopic appearance of the tumor found at autopsy. Note the uniformly spindle-cell character of growth. (Low power; hematoxylin and eosin stain.)

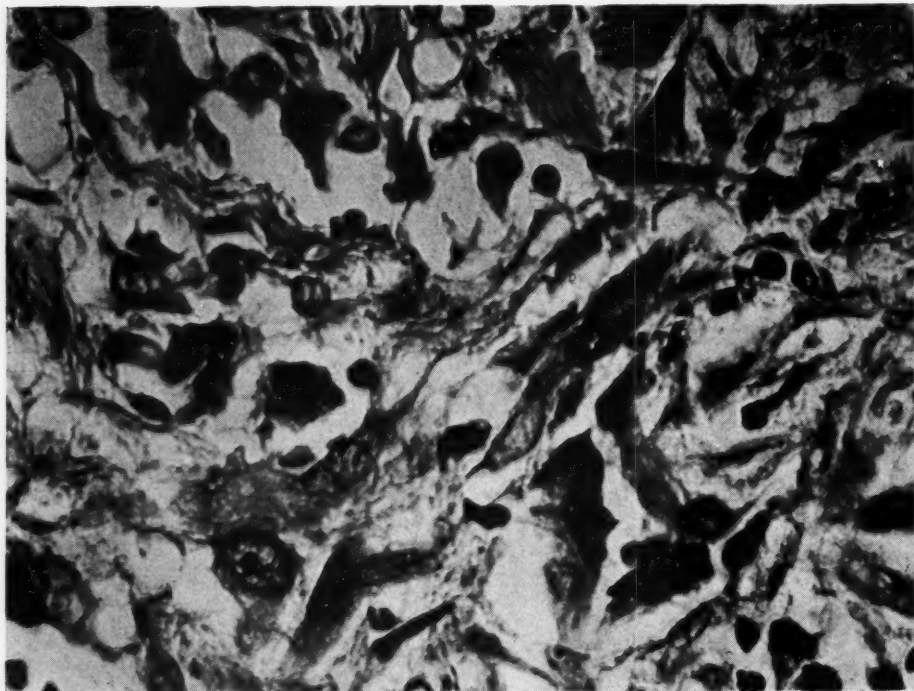


Fig. 3.—Section from another area of tumor found at autopsy. Note that cells in this area are pleomorphic. (High power; hematoxylin and eosin stain.)

The pericardial friction rub disappeared after two days. On April 1, 1949, it was noted that the patient had basal moist râles and a loud pleural friction rub over the right side of the chest anteriorly. The liver edge became palpable one and one-half fingerbreadths below the right costal margin. The patient failed rapidly and died on April 3, 1949.

Necropsy Report.—A large, hard, solid, white mass 10 cm. in diameter was found retroperitoneally at the level of the lower pole of the left kidney and separate from it. Within this mass was a short segment of the ureter. The left kidney was hydronephrotic. Other masses similar but of smaller size were found in the lesser omentum. The liver was studded with discrete, circumscribed nodules. Metastases were found also in the lungs. These were particularly extensive on the visceral and parietal pleurae. Large masses of tumor-involved nodes were found along the entire aorta. A tumor nodule was seen in the myocardium. Large amounts of fluid filled both pleural cavities; in the right cavity it was bloody and in the left cavity it was yellow. The spleen, pancreas, adrenals, gastrointestinal tract, kidneys and urinary bladder were not involved. The uterus, tubes, and left ovary were atrophic. A small tumor nodule could be seen in the right ovary. The vertebral marrow appeared normal to the naked eye.

Microscopic examination showed the tumor tissue everywhere to have essentially the same characteristics: it was richly cellular; mitoses were numerous; cells varied considerably in size and shape but were predominantly spindle shaped or elongated (Fig. 2); many cells were quite bizarre and a few were multinucleated (Fig. 3); the stroma was, for the most part, scant. Only after microscopic examination was the bone marrow seen to contain metastases. Myeloid metaplasia was noted in the spleen.

The anatomic diagnosis was metastatic granulosa-cell tumor (sarcomatous variety) involving pleura, lung, liver, abdominal lymph nodes, bone marrow, right ovary, and heart; bilateral pleural effusions and myeloid metaplasia of the spleen.

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ASSOCIATED POSTOPERATIVE VESICO- AND RECTOVAGINAL FISTULAS

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ALTHOUGH the literature and gynecologic texts contain many reports and discussions of vesicovaginal fistulas and rectovaginal fistulas occurring separately, there is scant mention of both types associated concomitantly.

The occurrence of both fistulas in the same patient as a postoperative complication of hysterectomy is extremely rare. Because of this rarity, and because of the problems which presented themselves in order to effect a cure, the following case is reported.

On May 7, 1948, the author was called in consultation into an outlying Chicago hospital to see a very distressed patient who was losing both urine and stool per vaginam. Mrs. F. S., aged 43 years, had entered the hospital on April 5, 1948, complaining of lower abdominal pain and irregular uterine bleeding. The past history and general physical examination were negative. The preoperative diagnosis was multiple uterine fibroids. On April 6, 1948, a total abdominal hysterectomy was performed. Right salpingo-oophorectomy was done at the same time for a corpus luteum cyst. The left tube and ovary were normal. The uterus was enlarged by multiple fibroids to the approximate size of a ten weeks' gestation. The largest tumor was on the posterior wall of the uterus just above the region of the internal os, and was adherent to the anterior wall of the rectum. No technical difficulties were encountered at surgery. The vaginal vault was closed without drainage by interrupted catgut sutures, and the patient left the operating room in good condition. The pathologic report confirmed the clinical diagnosis. A retention catheter placed into the bladder during the preoperative preparation was removed on the fourth postoperative day, after which the patient voided spontaneously. On this day she also had a normal bowel movement. The first five postoperative days were febrile with temperatures up to 101° F., the pulse varying between 72 and 88. The patient was discharged on the seventh postoperative day, afebrile, and feeling well.

Two weeks after leaving the hospital or on the twenty-first postoperative day she took an enema and described the result as "violent." After expulsion of the enema, she noticed "water and gas" escaping from the vagina. She was readmitted to the hospital for study. Stool-stained fluid and gas continued to escape from the vagina, but the patient urinated a fair amount via the urethra. On May 5, 1948, or one month following surgery, cystoscopic examination revealed a minute defect medial to the right ureteral orifice. A ureteral catheter was passed into this defect and appeared in the vagina. Speculum examination revealed a small figure-of-eight shaped "granulating" area in the apex of the vagina which was high. This area harbored two small openings from one of which poured urine. A uterine sound was passed through the other opening and could be felt in the rectal lumen about 10 cm. above the anal ring. The diagnosis was then obvious. The patient was instructed to wait for three months following the hysterectomy before repair of the fistulas should be attempted. However, her mental condition became so bad that on June 19, 1948, or about two and one-half months after operation, operative repair of the fistulas was performed after three days of preparation with sulfaguanidine and penicillin. Before continuous spinal anesthesia was started, the vesicovaginal fistula was threaded with a ureteral catheter through a cystoscope, and the rectovaginal fistula

was likewise threaded, with the aid of a short proctoscope (Fig. 1). The abdomen was opened after excision of the linea alba scar. The vaginal vault was identified by intra-vaginal pressure against the dome with a sponge stick by an assistant. With the vagina thus stretched the reflected bladder peritoneum was incised transversely and a line of cleavage between adherent rectum, bladder, and vagina was found. The top of the vaginal vault was grasped with vulsellum forceps. By blunt and sharp dissection, the bladder was mobilized completely from the anterior vaginal wall. The openings in the bladder and vagina were easily identified by the ureteral catheter, which was then removed through the vagina by an assistant. The bladder defect was invaginated with two layers of No. 0000 chromic catgut. The rectum was likewise dissected free from the posterior vaginal wall. The hole in the rectum was easily identified by the threading catheter, which was removed through the anus by an assistant. The rectal defect was invaginated by two layers of No. 0000 chromic catgut. The vaginal defects were then closed and the reflected bladder peritoneum was sutured to the rectal wall above the repaired fistula. After closure

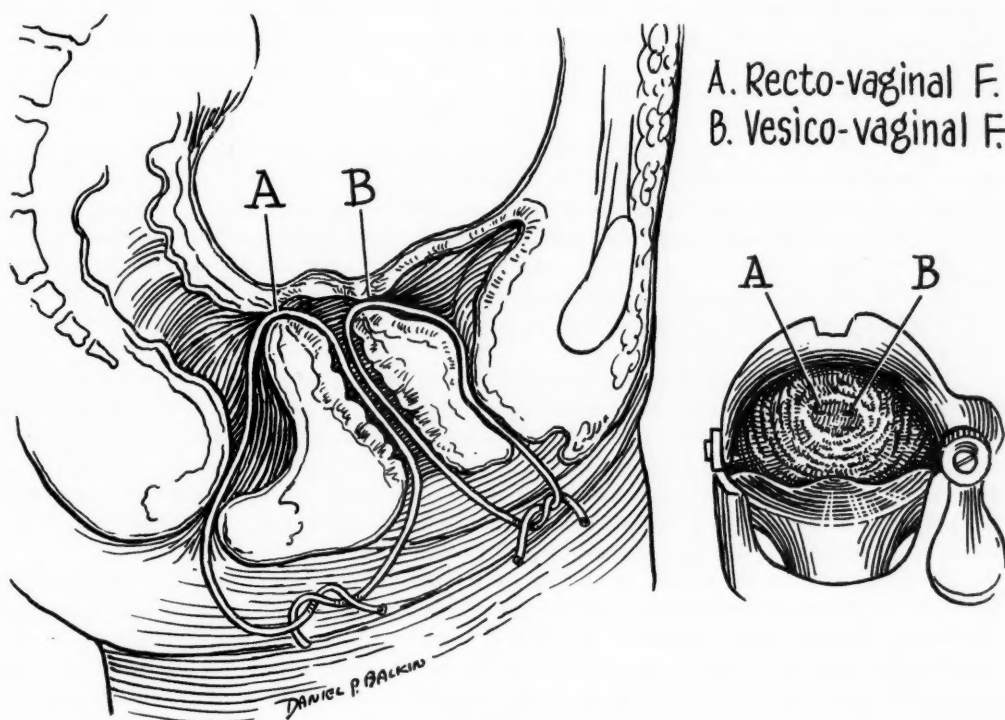


Fig. 1.

of the abdomen, a Foley catheter was introduced into the bladder, and a "dumbbell" was placed in the anal sphincter. In this manner, decompression of the bladder and rectum was assured. The patient had an uneventful postoperative course. The catheter was removed on the tenth postoperative day, and the patient was discharged on the fourteenth postoperative day. There was complete recovery of normal bowel and bladder function.

Most postoperative fistulas in gynecologic surgery are singular, either vesicovaginal or rectovaginal. It is rare for these two fistulas to occur concomitantly in the same patient. When such a situation arises, the case requires careful study and planning before surgery is undertaken. The identification of the fistulous tracts, especially when the repair is done transabdominally, is of paramount importance. A method of accomplishing this is demonstrated in the above case report.

SPONTANEOUS AMPUTATION OF A DERMOID CYST FROM THE OVARY

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IN THE reported cases of spontaneous amputation of ovarian tumors, the corresponding ovary and not infrequently the tube remain connected with the tumor. The simultaneous involvement of the adnexa in twisted ovarian tumors is very typical. On the other hand ovarian cysts which separate from the tube and ovary to become parasitic tumors are very unusual. In the review of the literature only three authors, Blackwell,¹ Hengge,² and Sugasti,³ were found who describe such an occurrence. In all cases the tumors were dermoid cysts. Because of the rare occurrence and the interesting mechanisms involved, a similar case is reported here.

A. F. (190675), a 36-year-old white, married woman, gave the history of an attack of severe abdominal pain, following a pelvic examination, which lasted one day but left the patient with some tenderness in the lower abdomen. Previously the patient had had a normal delivery three and one-half years ago and had enjoyed good health. About six years ago a left ovarian cyst was diagnosed and an operation was suggested but refused by the patient. The patient had no gynecological complaints until five months before admission when her menstruation became more frequent and some dull aching sensation in the lower abdomen was noted.

The examination showed parous external genital organs, a healing cervix after recent cauterization for an ectropium and cervicitis, the uterus in mid-position, of normal size and consistency, the right adnexa slightly tender without palpable abnormality. Left and in front of the uterus was a doughy cystic tumor of the size of a large fist. A tentative diagnosis of a dermoid cyst was made which was confirmed by an x-ray plate of the pelvis which showed a radiopaque part with an incisor-like tooth. The rest of the physical examination and laboratory findings did not reveal anything remarkable.

One month after the attack, a laparotomy was performed and a cyst of about 10 cm. in diameter was found in the left side of the pelvis. After some fine adhesions to the pelvic wall and broad ligament were separated by hand, the cyst could easily be delivered, appearing only broadly attached to the omentum. The left ovary from which the cyst had separated had a stumplike protrusion from its mid-portion but appeared otherwise of normal size and position. The left tube was intact and there were no bleeding points noted. The cyst was removed by resection from the omentum. It had the appearance of a dermoid cyst, slightly grayish in color, but showed no signs of infarction. The right ovary, containing a mature corpus luteum and a chocolate cyst of about 3 cm. in diameter, was resected, leaving two thirds of the ovary. The bladder peritoneum and the right broad ligament to which the chocolate cyst was adherent showed numerous pinpoint bleedings typical of recent endometrial implants. Suspension of the uterus by advancement of the bladder peritoneum, to prevent a fixed retroflexion of the uterus, and appendectomy concluded the operation. The patient made an uneventful recovery and was discharged on the ninth postoperative day.

Gross Examination.—The specimen consisted of an opened ovarian cyst, evacuated of its content, measuring 6.5 cm. in its greatest diameter. There were a few fatty and granular adhesions of the capsule. The wall of the cyst was smooth and in one area there was a raised and ovoid mound covered by hairy skin measuring 3.5 by 2.7 by 1.8 cm. Beneath there was some fibrofatty tissue and hard bony material plus a definite incisor-type tooth, the latter protruding above the surface.

Microscopic Examination.—Sections of the cyst showed degeneration of the wall with most of the epidermal mucosa desquamated or absent. Within the wall proper were seen epidermal derivatives, small areas of hemorrhage, follicular and sebaceous glands. Beneath there was considerable fibrofatty tissue showing inflammatory changes and containing scattered histiocytic cells with a lipoidal cytoplasm and infrequent giant forms.

The description of the resected cyst of the right ovary and the appendix were consistent with indirect endometriosis and atrophy of the appendix.

The formation of a pedicle between the ovary and the dermoid cyst which enabled the cyst to separate without disturbing the adnexa is an unusual finding. The pedicle must have developed gradually, as in the cases of subserous uterine fibroids, which amputate not infrequently. The pull of the cyst with its heavy content was probably the factor which led to the elongation and narrowing of the pedicle before the final amputation. This gradual separation and simultaneous weaning from the ovarian blood supply before separation seem to be confirmed by the absence of infarction usually seen in ovarian tumors with twisted pedicles. This case shows that a dermoid cyst can separate from the ovary without disturbing the adnexa and might be found free or attached to various abdominal organs. Such findings might cause confusion regarding the origin of the cyst if the possibility of the amputation from the ovary is not considered.

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HIDRADENOMA OF THE VULVA

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HIDRADENOMA is a growth, almost invariably benign, originating in sweat glands, and is synonymous with terms such as syringocystadenoma, sweat gland adenoma, and adenoma hidradenoides. This is considered a relatively rare tumor of the vulva, undoubtedly a conclusion derived from the fact that approximately only sixty cases have been reported in the literature since the original communication by Pick in 1904¹. The authors feel, however, that this entity occurs far more frequently, but is seldom reported and at times not recognized.

CASE 1.—A 60-year-old white woman had a pedunculated, hard mass attached to the right labium for "the last few years" prior to hospital admission. It was not painful, but seemed to have increased in size during the last few months. The tumor, which measured 10 by 4 cm. in size, was believed to be a fibroid and was excised under local anesthesia. Pathological examination showed an adenoma of sweat glands measuring 4.5 by 3 by 2 cm.

CASE 2.*—On routine examination of a 63-year-old white woman, a cauliflower-like nodule about 1 cm. in diameter was found on the right labium, which bled easily with even very gentle manipulation. A basal-cell carcinoma was diagnosed clinically and a hemivulvectomy performed. Pathological examination revealed two hidradenomas, one measuring 0.5 cm. and the other 1.0 cm. in diameter.

CASE 3.—For five to six years prior to seeking medical advice, this 64-year-old white woman noticed a hard, nontender mass the size of a "walnut" at the superior end of the right labium. It was asymptomatic, except for possibly a slight increase in size. A hard, bluish nodule measuring 2 cm. in diameter was excised under local anesthesia. Pathological examination established the diagnosis of papillary syringocystadenoma or hidradenoma.

CASE 4.—A 62-year-old white woman was admitted to the hospital because of a symptomless growth of the right vulva of "years'" duration. No clinical features of the lesion in situ were available. Simple excision under local anesthesia was effected. Pathological examination described a nodule measuring 2 by 2 by 1 cm. which was called "adenoma of the vulva, papillary cystic type." However, the histological description fitted diagnosis of hidradenoma. Review of the slide reclassified it as such.

CASE 5.—Routine examination of a 60-year-old white woman revealed a papillomatous growth of the right labium the size of a cherry. Therapy consisted of simple excision under local anesthesia. Pathological examination described a tumor with dimensions of 1.4 by 1.2 by 0.4 cm. diagnosed as an "adenoma of the vulva." Again, the microscopic description typical of hidradenoma of the vulva prompted review and reclassification of the slide.

The true nature of the lesion in this series was not suspected prior to histological examination. The failure to diagnose the cases properly is attributed to the wide range of gross, clinical manifestations of the tumor. No set of characteristic features can be outlined. The size of the lesion may vary from 1 to 10 cm. in its greatest diameter; the color may not be constantly that of normal skin, as in one of our cases it had a bluish pigmentation; the base may be sessile or pedunculated; the configuration ranges anywhere between a rough papillomatous to a smooth nodular appearance; the consistency is variable and, finally, the growth may present as a freely moveable, well-defined entity, or as a fixed, ulcerated, slightly raised, easily bleeding structure that is readily mistaken for a dermal carcinoma.

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*Case 2 was taken from the surgical pathology material in the Rhode Island State Hospital, the remaining four cases from the Rhode Island Hospital.

ARRHENOBLASTOMA BEFORE PUBERTY

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BECAUSE most of the reported cases of arrhenoblastoma occur in patients between the ages of 16 and 66 years, after puberty and the menarche, we are presenting a case in which symptoms began when the patient was 13½ years of age, just as puberty was being established.

A white American schoolgirl, aged 14 years and 1 month, presented herself on June 6, 1942, complaining of a deep voice of nine months' duration, of pimples on her face for seven months, and of the fact that menstruation, which began for the first time two months before, had been continuous in small amounts daily till it stopped one week before she sought medical advice. She stated that in the past year her desire for water had increased.

The patient was doing well in her schoolwork and was active in extracurricular activities. Until her voice began to take on masculine qualities, she had sung soprano in the school chorus.

The patient, an only child, stated that her father and mother were living and well. No familial disease was recalled. The patient had suffered from measles, chicken pox, scarlet fever, whooping cough, tonsillitis, influenza, and pneumonia. She had had a tonsilectomy and adenoidectomy in 1940. For several years the patient had been under care of an ophthalmologist because of a right internal strabismus and diminished visual acuity due to albinism with its concomitant lack of retinal pigment.

The patient was 64 inches tall and weighed 120 pounds. The temperature was 98° F. The girl had a very fair complexion due to albinism. She had pimples on her face and the back of the neck. Visual acuity was diminished due to lack of retinal pigment. Right internal strabismus was present. Hearing was normal and eardrums were intact. Mouth was clean with good teeth. The tonsils had been removed. There was no adenopathy and the thyroid gland was not enlarged. The breasts were small in view of her general development. The lungs were clear. The heart had normal sounds and was not enlarged. The blood pressure was 120/80 and the pulse rate 96. There were no abdominal masses, enlarged organs, or areas of tenderness. The clitoris was several times larger than usual. No pelvic examination was done on this occasion but by rectum no adnexal masses could be made out. Skeletal and neurological examinations were normal.

On June 6, 1942, the urine was normal, red blood count 3,950,000, hemoglobin 78 per cent, white cell count 6,400, with a differential of 63 per cent neutrophils, 35 per cent lymphocytes, and 2 per cent monocytes. The urea nitrogen was 16 and the sugar 83 mg. per cent on a fasting blood specimen. The blood creatinine was 1.1 mg. per cent and the blood Wassermann, Kahn, and Kline tests were negative.

An x-ray showed a normal sella turcica and no other skull abnormalities.

The patient had no menstrual period in July, 1942. In August, 1942, she had a scant flow for two days and in September had a scant flow for one day.

On Nov. 9, 1942, a pelvic examination was done, and the right ovary was firm, smooth, and the size of a large English walnut. The clitoris was several times larger than the average.

In the month of November, 1942, an excretory urogram showed no kidney displacement, and there was nothing to suggest adrenal tumor. The basal metabolism rate was -1. The blood cholesterol was 169 mg. per cent. At this time, the red blood count was 4,980,000 with 89 per cent hemoglobin and an 8,000 white count.

In December, 1942, the patient was seen in consultation by Dr. E. Perry McCullagh, Endocrinologist at the Cleveland Clinic. The androgen test showed 7.4 mg. of total 17-

ketosteroids in a 24-hour urine specimen. This test was repeated in January, 1943, and this assay showed 6.3 mg. of 17-ketosteroids. While these assays were within normal range, Dr. McCullagh felt that clinical judgment dictated an exploratory operation.

On Jan. 18, 1943, the patient complained of pain in the middle of the back and low on the right side and of general aching all over the abdomen. No menstrual bleeding had occurred since September, 1942.

On examination at this time, no abnormal growth of hair was noted except some increase on the legs. The voice was deep. The clitoris was enlarged as before. On pelvic examination, there was tenderness over a right ovarian cyst of grapefruit size.

On Feb. 16, 1943, the late Dr. Tom Jones, of the Cleveland Clinic, operated upon the patient. The notes on the operation were dictated as follows: "There was a moderate amount of free pinkish-yellow fluid in the abdominal cavity. There was a cystic tumor of the right ovary filling the entire pelvic cavity proper and extending upward into the abdomen to the level of the umbilicus and it was adherent to the posterior pelvic wall. The cyst walls were grayish white and thickened. The tumor was multiloculated and predominately cystic but thought to be solid in some areas. The uterus and both tubes were normal. The left ovary was small, markedly whitened, and its surface was smooth, suggestive of considerable fibrosis. Both adrenal glands were palpated and were normal in size, shape, and texture. No tumor could be felt grossly.

"A low midline incision was made. The cyst was freed and delivered from the pelvis, during which procedure one locule ruptured with escape of yellow serous fluid. The right tube and ovary were excised by division and ligation of the infundibulopelvic, broad, and round ligaments, and the tube close to the uterus. The small tear in the peritoneum posteriorly which occurred during freeing of the tumor was repaired. The appendix was excised. It was not grossly diseased. The omentum was brought down and packed into the pelvis. The abdominal incision was closed in layers with catgut sutures."

Dr. Allan Graham, pathologist, examined the ovarian cyst and found two nodules on its walls. One nodule microscopically showed tissue that appeared to be ovarian and the other nodule contained a variety of cells, some of which looked like an attempt at the formation of testicular tubules. It was considered to be an arrhenoblastoma.

The patient recovered uneventfully from the operation that was done in Feb. 16, 1943, and on March 16, 1943, she had a menstrual period for $3\frac{1}{2}$ days.

On June 10, 1943, she reported that at 28-day intervals she was having menstrual periods of 4 to 5 days' duration. The hair which the patient had removed a few months ago from her legs had not returned. The clitoris was definitely smaller. The voice remained deep and masculine.

On Dec. 9, 1943, the patient reported continuing regular and normal menstrual cycles, the pelvic examination was as reported above for June, 1943, and the clitoris was smaller. The breasts were round and full and the voice still deep.

In June, 1948, at the age of 20 years, the patient was married. She became pregnant after the menstrual period of Jan. 11, 1949. On Oct. 6, 1949, she gave birth to a normal girl baby weighing 8 pounds, and 5 ounces.

Observed on March 23, 1950, the patient was 66 inches tall and weighed 127 pounds. She possessed delightful feminine charm and contours, had a continuing 28-day menstrual cycle, but was still in possession of the deep voice.

Summary

The case is unique in appearing at the early age of $13\frac{1}{2}$ years and in the development of symptoms concomitant with the establishment of puberty. The patient has been followed through marriage and the achievement of a normal pregnancy and the attainment of mature femininity.

TUBERCULOSIS OF ENDOMETRIUM AND OF CERVIX ASSOCIATED WITH PREGNANCY. SUCCESSFUL TREATMENT WITH STREPTOMYCIN

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UNSUSPECTED pelvic tuberculosis, particularly tuberculous endometritis, is not so uncommon as has previously been supposed.¹ It is frequently not associated with a demonstrable lesion elsewhere. Nevertheless, pregnancy imposed on such a situation is extremely rare.

Congenital aspiration tuberculosis in the newborn, though not uncommon, is usually reported in connection with pulmonary or generalized tuberculosis. However, the generalized infection may not be manifest in the mother prenatally² and apparently need not exist, as in our case.

Although the accepted treatment of genital tuberculosis is either radical surgery or irradiation³ a few reports lately of the use of streptomycin have seemed promising.^{4, 5}

The case reported here combines several factors of unusual interest, and the results apparently obtained with streptomycin seem particularly worth noting.

Mrs. J. B. C. was aged 26 years, gravida i, para 0. The menstrual history follows: Onset was at age 12 years, every 30 days for 4 to 5 days. The last menstrual period was May 11, 1948. The patient, the wife of a resident physician specializing in internal medicine, was certain that conception occurred on May 23, 1948. Shortly thereafter, she complained of fatigue, malaise, and low-grade fever. Physical and laboratory findings at this time were negative, and the symptoms disappeared in about one week. The pregnancy was uncomplicated except for a slight pinkish vaginal discharge in the thirtieth week, due to a badly eroded cervix. This continued until the onset of labor about four weeks later. Labor was normal, and an apparently normal male infant weighing 5 pounds, 14 ounces was delivered Jan. 9, 1949. About seven hours after delivery, the patient's temperature rose suddenly to 103.6° F., and she had a drenching sweat, but no chill. For the next five days she had a temperature rise twice daily, but no chills, and the peak was 104.6° F. All laboratory studies were negative, including blood cultures, stool examinations, agglutinations, malaria smears, urinalyses, and repeated blood counts. There was no evidence of thrombophlebitis, and pelvic examination was negative. The chest x-ray was negative except for a suggestion of atypical pneumonitis. Sulfadiazene and penicillin were given for five days without affecting the fever, and streptomycin 1 Gm. daily in four divided doses was given from Jan. 12 until Jan. 17, 1949. At the end of this time the temperature became and remained normal, and the patient left the hospital on Jan. 19, 1949, apparently well.

The baby appeared normal at the time of discharge from the hospital with the mother, but developed loss of appetite and returned to the hospital. There signs of pneumonia developed, and a chest x-ray revealed what appeared to be miliary tuberculosis. He became progressively worse, and died at the age of 22 days. Autopsy revealed widespread lesions throughout the lungs, but in no other parts of the body. The diagnosis was therefore aspiration tuberculosis. This case has been reported previously.⁶

Immediately after these facts were known, the mother had a complete physical examination by her internist, which was negative, and a chest plate taken on Feb. 1, 1949, was

also reported as negative. A pelvic examination on February 2 revealed a large, boggy, retroverted, subinvolved uterus with an eroded cervix which admitted the tip of a finger. Cultures from the endocervix taken at this time were positive on February 22 for acid-fast bacilli. A second culture taken on February 25 was also positive in 20 days.

Additional history was obtained after the death of the baby. The only possible contact with tuberculosis was when the patient was employed as an occupational therapist by the Veterans' Administration a year before marriage. At that time she came into contact with tubercular patients. Several chest films during that time were negative, as was her separation film in July, 1948, during the third month of her pregnancy. The husband has had a recent negative chest x-ray, and is in excellent health.

On Feb. 4, 1949, the patient was started on 1.0 Gm. of dihydrostreptomycin daily. Throughout the course of treatment (120 days), she did not exhibit any fever, and there were no signs of toxicity referable to the drug. Her husband kept a careful temperature and progress chart.

At the time the diagnosis of pelvic tuberculosis was first made, no reports of the efficacy of streptomycin were available. Advice as to the method of treatment varied. A number of gynecologists suggested surgery. Both Curtis⁷ and Novak⁸ suggested conservative treatment in view of the findings, but felt that surgery might be indicated later. Internists consulted were generally in favor of streptomycin therapy. Because of the age of the patient, her desire to bear children, and the expressed wish by her and her husband to avoid surgery if possible, a conservative regimen was undertaken, and, after evidence of improvement, continued. There was some criticism of the frequency of curettage of the uterine canal, but we felt that we had no other means of checking our results satisfactorily. It is impossible to say whether or not the tubes were involved, but the patient conceived without difficulty, and at no time, even under anesthesia, were adnexal abnormalities felt. Culdoscopy was deemed unnecessary.

Following is a condensed outline of the procedures done during the course of the treatment. Curettements were done as nearly as possible one or two days prior to the expected beginning of a period.

March 26, 1949.—Curettage and biopsy of cervix. Report of pathologic examination, "Histological findings typical of tuberculosis; tuberculous cervicitis and endometritis." A guinea pig was inoculated with material from the endometrium, and was killed on May 31, 1949, and was positive for tuberculosis.

April 8, 1949.—Pelvic examination, uterus normal in size, retroverted; cervix still eroded, but much improved. Pessary inserted.

May 2, 1949.—Pessary removed, smears taken from high in cervical canal. Cultures from these swabs negative.

May 14, 1949.—Curettage and biopsy of cervix (99 days after dihydrostreptomycin was started); much less endometrial tissue obtained than formerly. Report of pathological examination, "Number of tubercles considerably less than in previous specimen." Tuberculosis of the endometrium was still present, but the cervix showed only a benign erosion. Cultures and guinea pig inoculations from the uterine cavity were negative.

June 4, 1949.—Dihydrostreptomycin discontinued.

July 13, 1949.—Curettage and biopsy of cervix. Report of pathological examination, "Normal endometrium, benign cervical erosion." Guinea pig inoculated with endometrial material and killed 81 days later with no evidence of tuberculosis. Cultures also negative.

Several examinations revealed normal-appearing cervix, no vaginal discharge, normal menses.

Nov. 12, 1949.—Curettage. Pathological report, "No evidence of tuberculosis at this time, normal secretory endometrium." Two guinea pigs inoculated, and found to be free of tuberculosis at death, 3 and 4 weeks later.

Dec. 9, 1949.—General physical examination and chest x-ray negative. Pelvic examination normal except for asymptomatic retroversion.

We plan routine pelvic examinations and cultures as follow-ups, but no further curettements unless some clinical developments indicate them. If the patient is clinically well, and cultures are negative for another year, we may allow pregnancy, since the patient and her husband are fully cognizant of the risk involved.

We do not think that a definite place can yet be assigned streptomycin in the treatment of tuberculosis of the female pelvis, but the evidence to date is that it is of definite benefit. Further evaluation must wait on the reports of a number of cases such as this one, and those previously reported, with follow-up observations over a period of years.

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Department of Book Reviews

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Review of New Books

Gynecology

A collection of thirteen authoritative discussions on subjects related to the physiology of menstruation is presented in **Menstruation and Its Disorders**.¹ Five of the first six subjects deal with enzymatic or chemical processes within the endometrium, cervix, or ovary. Investigations based on studies of Atkinson, Engle, and Elftman demonstrate a relationship between alkaline phosphatase and the ovarian hormones, the enzyme being increased by estrogen and diminished by progesterone. George B. Wislocki discusses methods for demonstrating phosphatases, glycogen, lipoids, cytoplasmic basophilia and metachromasia in the cervix. G. Gomori summarizes with meticulous care the technical steps required for the demonstration of tissue lipase. Descriptions of very early abortive human ova are given in a beautifully illustrated paper by A. T. Hertig and J. Rock.

Of particular significance is the presentation of the so-called Schlegel theory of menstruation based on Okkel's description of arteriovenous shunts around peripheral endometrial capillaries. J. Markee describes studies in monkeys showing a relationship between rate of blood flow in the endometrium, ovarian steroids, and menstruation.

Two chapters are devoted to menstrual toxin, whereas only casual reference is made to the endocrinology of the menstrual cycle. There is a very brief discussion of functional bleeding with emphasis on the etiology of hyperplasia. This book will be found a valuable reference source for all investigators in the broad field of human reproduction though its technical nature may prove confusing to the busy clinician.

GARDNER M. RILEY.

This **Textbook of Endocrinology**² was written by the editor in collaboration with eleven other authors selected on the basis of contact with both basic and clinical investigations as well as experience in particular medical specialties. In addition to the presentation of etiology and treatment of definite endocrine disorders, the editor has chosen to give considerable attention to disease entities that are sometimes mistakenly thought to be endocrine in origin. The viewpoint is taken that since these conditions frequently fall into the clinical province of the endocrinologist, this specialist should be prepared to deal with them. Obesity falls in this category and is discussed concisely and authoritatively by L. H. Newburgh.

In general the clinical aspects of endocrinology are presented with exceptional clarity by the several collaborators. Particularly commendable are the discussions of disorders of the thyroid, parathyroids, adrenals, and pancreas. Although each of these glands has been the object of the most intensive investigations during recent years, the authors have blended

¹**Menstruation and Its Disorders.** Proceedings of the Conference held under the auspices of The National Committee on Maternal Health, edited by Earl T. Engle, Ph.D., College of Physicians and Surgeons, New York. 358 pages with 105 illustrations. Springfield, Ill., 1950, Charles C Thomas. \$6.50.

²**Textbook of Endocrinology.** Edited by Robert H. Williams, M.D., Executive Officer and Professor of Medicine, University of Washington Medical School, Seattle. 793 pages with 168 figures and 3 color plates. Philadelphia, 1950, W. B. Saunders Company.

in a creditably clear manner the purely investigative aspects of glandular physiology with the practical problems of clinical endocrinology.

The first chapter includes a short discussion of the general principles of endocrinology and is followed by chapters dealing with the pituitary, thyroid, adrenals, testes, ovaries, pancreas, and the parathyroids. One chapter by Lawson Wilkins deals with the complexities of somatic growth and includes tables of normal measurements as well as a useful tabulation of osseous development.

The chapter on the adrenals is divided into two parts: the first by the late Dr. E. J. Kepler deals with hyperadrenal-corticalism and hyperfunction of the medulla, the second by Drs. Thorn and Forsham covers adrenal cortical insufficiency. The section on the testes is entirely of a clinical nature.

The neuronendocrine and psychodynamic aspects of endocrinopathies are presented in more detailed fashion than is usually encountered. Harry B. Friedgood presents a most complete summary of the literature on this subject. The chapter includes three hundred references, which is more than the total for the first five chapters of the book.

The physiology of human reproduction, menstrual dysfunctions, and pregnancy are combined under the heading of "The Ovaries." Probably because the chapter necessarily includes so many diverse subjects, from the regulation of anterior pituitary function by theoretical toxic agents to the hormonal treatment of breast cancer, it tends to be somewhat confusing to the reader. Written by George Van S. Smith, the presentation is understandably colored by this author's many years of active investigation in this field. This section includes a brief but useful discussion of sterility.

The final chapter, entitled "Laboratory Diagnostic and Assay Procedures," appears rather superfluous since, as the author points out, various clinical tests were discussed earlier in the text, no effort is made to discuss the historical development of the tests, and the technical details of the various methods are not given.

This is an entirely up-to-date presentation of endocrinology and metabolism for the more advanced medical student and especially for the physician who deals with clinical endocrinopathies.

GARDNER M. RILEY.

The second edition of Janney's **Medical Gynecology**³ is noteworthy for its successful combination of practical clinical information with the fundamental physiologic and pathologic concepts of the subject. After an introductory discussion of methods of history taking and routine physical examination, the author presents a series of chapters dealing with the presenting complaints of patients, arranged under headings listing physiologic and pathologic causes of each complaint. This method results in a certain amount of repetition, but has the advantage of rendering each section independently useful and convenient for reference. In less detail, subsequent sections deal with physical findings, laboratory and other special methods, and gynecologic office treatment.

The outstanding feature of the book is its unusually complete and constructive discussion of such socioeconomic problems as touch on the gynecologist's field of practice: birth control, sterilization, abortion, illegitimacy, sex hygiene. The sections on marriage counseling and the management of marital maladjustments clearly reflect a special interest in and experience with this too often neglected phase of gynecology. New to this edition are chapters on metrorrhagia, culdoscopy, cytologic methods, recent modifications of pregnancy tests, and the medicolegal problems involved in such controversial subjects as artificial insemination, and therapeutic abortion in cases of rubella. There are also careful discussions of penicillin and sulfonamide therapy, and briefer mention of the uses in gynecology of the newer antibiotics. The appended bibliography is meager and superfluous; a few selected references to the recent literature on topics which could be mentioned only briefly in the text might have been helpful in some connections. An exhaustive bibliography would obviously be out of place in a work of this sort.

³**Medical Gynecology.** By James C. Janney, M.D., F.A.C.S., Associate Professor of Gynecology, Boston University School of Medicine; Associate Visiting Gynecologist, Massachusetts Memorial Hospital. New, second edition. 454 pages with 108 figures. Philadelphia and London, 1950, W. B. Saunders Company. \$6.50.

The book is well printed, serviceably bound, and fairly well illustrated, chiefly with figures from other standard works. It should be of especial value to the medical student making the transition from the didactic course to work in the clinic and on the wards, correlating as it does the basic sciences with clinical diagnostic procedure. The general practitioner will find it a concise, reliable, and thoughtful compendium of current practice in office gynecology. The gynecologic specialist should have it primarily for its exceptionally sane and sympathetic approach to the emotional side of his office practice.

DOUGLAS M. HAYNES.

The subtitle of this excellent clinical survey of gynecology⁴ states that it is "The Teachings of John I. Brewer." Consequently, the book should be reviewed from this highly personalized aspect. It was written with two purposes in mind: "The first is to arrange and present the gynecologic entities and related conditions according to the manner in which they can be utilized best in the making of clinical diagnoses, in the treatment of patients, and in the teaching of gynecology. The second purpose is to present sufficient essential information about each disease so that one can learn basic clinical gynecology and can develop a pattern of thinking which will expedite and make more efficient the examination and treatment of patients." Admittedly the book is didactic and aims to present the thinking and practices of a single group. Dr. Brewer says, "We acknowledge the right and value of opposing schools of thought, and we offer this material not as the only way to think and do, but simply as our way."

The arrangement of the chapter headings is certainly new and novel, and time alone will reveal whether or not it will receive general accord. For example, the titles of the first seven chapters are: Asymptomatic Pelvic Tumors, Pelvic Tumor With Abnormal Uterine Bleeding and Without Pain, Pelvic Tumor With Abnormal Uterine Bleeding and With Pain, Pelvic Tumor With Pain and Without Bleeding, Abnormal Uterine Bleeding Without Pain and Without Palpable Tumor, Bleeding and Pain Without Tumor, Pelvic Pain Without Tumor and Without Abnormal Bleeding. This type of division necessitates frequent repetition which Dr. Brewer believes is good pedagogy. The remaining ten titles indicate a more conventional type of arrangement. There are but 15 references and 66 illustrations in the entire volume. Perhaps in a second edition it will be possible to increase the number of illustrations.

The second purpose of the book is admirably achieved. Dr. Brewer's gynecologic teachings and practice are sane and sensible, and this reviewer can find only praise for the courageous stand taken on many subjects. There is no equivocation and no doubt at all concerning the personal beliefs and preferences of the author. Of special noteworthiness are the frequent tabulations of reasons for treatment. A subject is discussed, and operative treatment recommended, "if": then follows a tabular series of pertinent statements. This feature should appeal to busy practitioners who want a definite answer to a specific problem.

Dr. Brewer is a master gynecologist. He has set down in a book his personal beliefs, principles, and practices in the field of gynecology. These can be accepted with the conviction that they represent the author's teachings. Since this reviewer subscribes to almost all of these teachings, he has no hesitancy in recommending the book to medical students, interns, residents, and to the general practitioner to whom it is obviously directed.

WILLIAM F. MENGERT.

This book⁵ is the result of a series of gynecological lectures given by the authors to medical students. The second edition has been entirely revised since 1939. Additional in-

⁴**Gynecology.** The Teachings of John I. Brewer. John I. Brewer, B.S., M.D., Ph.D., Professor of Obstetrics and Gynecology, Northwestern University Medical School; Chief of Gynecology and Obstetrics, Passavant Memorial Hospital, Chicago. 437 pages with 66 illustrations. New York, 1950, Thomas Nelson & Sons. \$7.50.

⁵**Gynaecology.** By Herbert H. Schlink, M.D., Ch.M. (Sydney), F.R.A.C.S., F.R.G.S., Honorary Consulting Gynaecological Surgeon, Royal Prince Alfred Hospital, Sydney, and Clement L. Chapman, D.S.O., V.D., Med. des Epid., M.B., Ch.M., (Sydney), F.R.C.S. (England), F.R.C.S. (Edinburgh), F.R.A.C.S., Clinical Lecturer in Gynaecology, and George G. L. Stening, E.D., M.B., B.S. (Sydney), F.R.C.S. (Edinburgh), F.R.A.C.S., M.R.C.O.G. (England) Lecturer in Gynaecology, University of Sydney, and Frederick N. Chenhall, M.B., B.S. (Sydney), F.R.C.S. (England), M.R.C.P. (Ireland), F.R.A.C.S., Clinical Lecturer in Gynaecology, University of Sydney. Second Edition. 650 pages with 198 illustrations and 19 color plates. Sydney, Australia, 1949, Angus and Robertson. Price 67 s., 6 d.

formation on anatomy, endocrinology, menstrual disorders, cancer, operative procedures, and virilism has been included. Although there is only superficial treatment of many subjects the contents are well presented in thirteen chapters. The chapters on anatomy and physiology are very informative. The difficult subject of gynecologic pain is comprehensively covered.

The chapter on malignant growths is of marked interest. The authors use 5,000 to 7,000 mg. hr. of radium to treat all carcinomas of the cervix. A Wertheim radical hysterectomy is routinely done following radium therapy. Their Wertheim operability rate is 50 per cent of all cervical carcinomas. An over-all death rate of only 4.9 per cent has resulted from 367 Wertheim procedures. Pelvic glands were involved in 20 to 25 per cent of all cases. X-ray therapy is not given. The authors firmly believe that most patients with cervical carcinoma should have a Wertheim operation following radium treatment.

All surgical procedures are grouped into one chapter which is markedly deficient in suitable illustrations. The Manchester operation is well described, but the Wertheim procedure is barely mentioned. The authors err in ascribing the popularity of the extraperitoneal cesarean section in America to "the Chicago group."

Postoperative treatment and complications are lucidly discussed. Patients are still kept in bed for 17 days after surgery before they are ambulatory. Intestinal obstruction and venous thrombosis data are interestingly presented.

Subject references are notably absent throughout the entire book and a bibliography is not included. Most of the subject matter is a summation of the authors' wide gynecological experiences.

Gynaecology is an easily read, well-presented text, and is broadly inclusive of its subject. It can be well recommended to the medical student and practitioner.

RICHARD L. HERMES.

The first presentation of Robert Schröder's *Gynäkologie*⁶ appeared in 1922, the preparation of which followed the cessation of World War I. The book met with success and a revised edition was published in 1926. As stated in the preface, Schröder postponed a further revision for many years, so that his material might "ripen," as he says. Consequently he now presents a third and fourth edition as one—essentially a complete rewrite—following the armistice of World War II.

Gynecologic disorders are presented on an etiological basis. The text is comprehensive, thorough, and meticulous in preparation, and is an excellent treatise for the medical student and general practitioner, with fundamental information for the specialist as well. The volume is arranged in nineteen sections, beginning with the initial consultation, examination, and analysis of the problem at hand. The work progresses systematically through the structure and function of the genital organs, with special emphasis upon the menstrual cycle, hormonal activity, and its histologic implications, to the early understanding of which Schröder contributed so much.

Uterine displacements and their management, and the part really played by abnormalities of the vulva, vagina, and cervix with respect to the well-known symptomatic triad of *Blutungen*, *Ausfluss*, and *Schmerzen*, attributed in bygone days to "chronic endometritis" are next discussed. In sequence follow the sections devoted to pelvic infections as we generally understand them; endometriosis interna (rather than adenomyosis) and externa; sterility; developmental anomalies (including here physiologic cysts of the ovary and other types of retention cysts of congenital origin); true neoplastic cysts and tumors of the ovary; myoma and sarcoma.

Part XVII is devoted to carcinoma of the uterus, vagina, vulva, and tube. Much emphasis is placed upon the primary responsibility of the general practitioner in this regard. Office biopsy is discouraged, but cervical tissue scraping for diagnosis is recommended. Vaginal cytologic diagnosis is not mentioned. The final portions of the book refer to the relationship

⁶*Gynäkologie für Studium und Praxis*. By Professor Dr. Robert Schröder, Direktor der Universitäts-Frauenklinik, Leipzig. Third and Fourth Editions. 551 pages with 387 illustrations. Berlin, 1948, Springer-Verlag.

of urology to gynecology, and to the solicitude that the physician should exercise in his relationship with his female patients throughout the successive epochs in their lives.

Discussion of therapy is limited to indicated procedures as far as surgery is concerned, medicinal and mechanical procedures of office and institutional nature being mentioned in more detail. Reference to antibiotics is relatively brief but this is understandable since access to these agents was limited in Germany until recently. Sulfonamides receive more emphasis. It may be stated here as a matter of interest that Domagk of Elberfeld, discoverer of the early chemical Prontosil, was jailed by Hitler because of the Nobel prize which had been awarded him during the days of the Nazi regime.

The volume is reasonably well printed but the paper is not of prewar quality. Profusely illustrated, the excellent photomicrographs lose something in reproduction, but allowance must be made for these minor faults, for German publication and printing were just getting under way again when the book went to press in 1948. All in all, Robert Schröder's newest work is a fine one and it should be of distinct advantage not only to the German student and physician, but to others who wish to read or consult the text.

LEWIS C. SCHEFFEY.

The second edition of this, the best known French work⁷ on gynecological endocrinology, is dedicated by the author to his father, a pioneer in the field of endocrinology. The preface is from the pen of another well-known endocrinologist, Prof. H. Simonnet, with whom the author states that he began in 1936 the studies which in large measure form the basis for the present book. This fact, together with the fact that there has been no effort to review the vast literature, especially in the field of therapy, gives the book a distinctly personal touch, though some may think that it at the same time detracts somewhat from its value as a work of reference.

The text, embracing more than 450 pages, is divided into four parts. Part 1 is devoted to gynecologic physiology, and includes a very satisfactory discussion of the endocrinologic mechanism at the various life phases of woman. The reproductive hormones are much more extensively and meticulously discussed in Part 2, from both the experimental and clinical viewpoints. Part 3 has to do with methods of hormonal diagnosis. In addition to valuable data concerning standard bioassay findings at various life periods, there is a good discussion of such diagnostic aids as endometrial biopsy and vaginal smears. The small group of photomicrographs depicting various endometrial hormonal responses is well chosen. Finally, Part 4, comprising more than 200 pages, is devoted to the consideration of the hormonal diagnosis and the treatment of the various functional disorders encountered by the gynecologist.

In any work on endocrinology, especially one with such a personal complexion as this, minor criticisms will inevitably crop up in the minds of at least some readers. For example, I can imagine that some American endocrinologists may resent the multiplicity of indications which Bécélère finds for the employment of testosterone in the functional gynecological disorders, although others among us consider its "antiestrogenic" effects of definite value in certain disorders. Bécélère, of course, emphasizes the limitations of dosage necessary for the avoidance of any masculinization side effects. Again, Bécélère lays much more stress on bioassay in the clinical management of functional disorders than do most of our American clinicians. Still others might criticize his very frequent resort to hysterosalpingography, not merely for sterility, but for such functional disorders as habitual abortion and functional bleeding.

The presentation of the author's material is a model of method and system, each of the four parts being logically divided into convenient chapters, and each chapter in turn being subdivided into small subsections. The bibliography refers chiefly to French sources, mainly by the author and collaborators, and with a rather glaring neglect of the rich American

⁷*Diagnostic Hormonal et Traitements Hormonaux en Gynecologie.* By Claude Bécélère. Second edition. Preface by Prof. H. Simonnet. 460 pages with 17 figures. Paris, 1949, Masson et Cie.

and British modern literature in this field. On the whole, the work has well earned the popularity which it enjoys in France, and the American gynecologist who reads French will find much of interest and value in its pages.

EMIL NOVAK.

Aktuelle Probleme der Pathologie und Therapie is dedicated for the 125th year anniversary of the St. Georg General Hospital in Hamburg as a "Festschrift" and is written by the medical staff of the different departments under the direction of Prof. Dr. H. Holthusen. There are 23 papers dealing with different clinical, diagnostic, and therapeutic problems. One paper by Hauch is a report on the therapeutic effect of penicillin and "supronal." (This is a combination of two sulfonamide preparations and is effective on aerobic as well as on anaerobic organisms.) Twenty-two cases of severe septic conditions were treated and in three cases penicillin alone, in seven cases supronal alone, and in 12 cases penicillin and supronal both were administered. Ten patients were cured and nine died. In three cases of subacute bacterial endocarditis there were marked improvements observed. Another paper by R. Cordua discusses the occurrence of chorionepithelioma in multiparas and also near the term of pregnancy and with extensive metastases. The cases are presented without autopsy in comparison with several other cases in the literature with autopsy findings. Several cases of destructive invasive hydatidiform moles with benign histologic appearance were also presented. Unfortunately no references were included. One paper by Dr. Holthusen gives an extensive statistical review of the radiation treatment of different carcinomas of the female genital tract, including the carcinomas of the urethra.

The book is closed by a historical review of the Allgemeines Krankenhaus St. Georg by Prof. H. Holthusen.

JOSEPH STASNEY.

Miscellaneous

Fortunate indeed is it that Emil Novak and other friends of Robert Meyer persuaded the renowned gynecologic pathologist to prepare so agreeable an autobiography⁹ before death overtook him in his adopted country on Dec. 12, 1947. The autobiography first appeared in serial form in the *Journal of the History of Medicine and Allied Sciences* under the title, "A Short Abstract of a Long Life." It is difficult, in a brief review, to do justice to this simply written story of such an eventful life. In fact, Novak's most complete memoir, which serves as an introduction to the volume, is sufficient survey in itself, and almost tempts a reviewer to confine himself to quotations from it.

Much of the charm of the book, which Robert Meyer dedicated "To My Friends in the United States of America," lies in the story of his early life in the picturesque and cultural Germany of the nineteenth century, for every word breathes his love of those early days. Intimate family pictures make delightful reading. All were musically inclined, Robert himself doing well with the piano and violin, an avocation enjoyed throughout his lifetime. About 1887 he married his cousin—a happy union, terminated only by her death in 1941. Soon after marriage he began his medical education at Strassburg, where he early learned to cut microscopic sections by hand, his teacher being Von Recklinghausen, Rudolph Virchow's very first assistant. The thumb-nail sketches of his famous teachers are clear-cut and decisive.

Robert Meyer began practice as a country doctor and his experiences as such are frankly, but humorously told. The village was Dedeleben in Saxony, near the Harz mountains and his life there with his family was a joyous experience. When he was thirty years of age, the Meyers decided to go to Berlin, where soon afterward he became an assistant in Veit's clinic. His first literary contributions, dealing with gynatresia and hematocolpos, were pub-

⁸**Aktuelle Probleme der Pathologie und Therapie.** By Prof. Dr. H. Holthusen, Medical Director of the St. Georg General Hospital in Hamburg. 248 pages with 49 illustrations. Stuttgart, 1949. Georg Thieme.

⁹**Autobiography of Robert Meyer (1864-1947): A Short Abstract of a Long Life,** with a Memoir of Dr. Meyer, by Emil Novak, M.D. 126 pages with one illustration (photograph). New York, 1949. Henry Schuman.

lished in Veit's *Handbuch für Gynäkologie* (1897), following of course his initial "Inaugural Dissertation" in 1889. From then on Meyer's writings continued progressively in scope and character, his final bibliography amounting to approximately 250 publications. None were mediocre and many were epoch making, a result of prodigious labor and a brilliant intellect. It is quite well recognized that Meyer's work in embryology and the genesis and evaluation of ovarian tumors stamps the originality of his work, which has been of inestimable value and of world-wide benefit to the science and practice of gynecology. Students streamed into his laboratory from every land, carrying his influence everywhere. In addition to the carefully compiled bibliography, Meyer's histogenic classification of ovarian tumors likewise appears in the volume.

Veit had also worked with Carl Ruge, and when the former accepted a call to Leyden he recommended to Meyer that he make contact with Ruge at the University clinic. This friendly and understanding association was a lasting one until Ruge's death in 1926. The latter's influence in early cancer diagnosis is obvious in Meyer's published concepts. Especially interesting is his discussion of "erosion and pseudo erosion" on page 46. Earlier in the book is a statement that typifies Meyer's sound appraisal of scientific achievement, for in speaking of the controversial aspects of the etiology of endometriosis he says, "Who is right is of no importance; what is right is what matters." In 1908 he took over Bumm's laboratory at the "Charite" in Berlin and was designated Professor; later he rejoined him in the "Artilleriestrasse" as Prosector of the Pathological Institute, succeeding Carl Ruge there. This was his professional home for the rest of his life in Germany, interrupted by army service in World War I and terminated by Hitler's stooges, Rust and Frick, in 1938. Stoeckel, anti-Nazi head of the Universitäts Frauenklinik, protected him as long as he possibly could and Meyer pays a beautiful tribute to his chief's loyalty to him. In the chapter of the book entitled "The Sunset Years," Meyer writes simply but dramatically of the opportunity to come to America, made possible by the energy of Dr. J. L. McKelvey of the University of Minnesota, together with the aid of other American admirers. He taught and wrote in his new home, six articles appearing in American literature, and the book ends with the simple statement, "Since December 14, 1945, I have been a proud citizen of the United States of America."

In summary, the *Autobiography* is a generous combination of history, philosophy, and scientific achievement. From the latter aspect alone it can be heartily recommended for informative as well as pleasurable reading. I would go even further and state unequivocally that every gynecologist and obstetrician, and particularly pathologists, even those not having a major interest in gynecologic pathology, would do well to have this volume in their libraries.

LEWIS C. SCHEFFEY.

This volume, *Breast Deformities and Their Repair*,¹⁰ is written for the surgeon or gynecologist contemplating plastic surgery of breast deformities. The problem is approached from an anatomic, physiologic, and esthetic viewpoint. An attempt is made to detail a safe procedure for each individual problem. The material is clear and concise; the illustrations are adequate. In the light of his own experience the author evaluates and analyzes many procedures only to reject them as undesirable. Thus, for the sake of completeness, an otherwise satisfactory reference book is cluttered with descriptions of defunct procedures. Since those who will use this text are looking for commendable methods much of this would be better omitted. Despite this I like the book and recommend it in its narrow field.

LLOYD W. STEVENS.

This story¹¹ of the life of Elizabeth Blackwell, the first woman who attained the degree of Doctor of Medicine, gives also a fascinating if kaleidoscopic picture of the times in which

¹⁰*Breast Deformities and Their Repair*. By Jacques W. Maliniac, M.D., Clinical Professor of Plastic Reparative Surgery and Associate Attending Plastic Reparative Surgeon, New York Polyclinic Medical School and Hospital. 193 pages with 119 illustrations. New York, 1950, Grune and Stratton, Inc. \$10.00.

¹¹*Child of Destiny*. By Ishbel Ross, Newspaper reporter and novelist. 293 pages with a frontispiece. New York, 1949, Harper and Brothers. \$3.50.

she lived. Starting in Bristol, England, we are given a glimpse of the manners, customs, and political thinking in the England of that time. Each member of her family was an individualist and each was talented. One can easily picture the family atmosphere which might stir a young woman of imagination, courage, and strong convictions into becoming a pioneer.

Elizabeth Blackwell had exactly the right combination of intellectual attainments, idealism, dignity, and perseverance to enable her to win out in her very difficult struggle for recognition. She never forgot to behave as a lady should, no matter what the provocation. She enjoyed many avocations, was widely read, and was always careful of her appearance and dress. She believed that as a woman she understood the problems of women and children and felt firmly that her sex was of the greatest advantage to her. Her belief in family life, her happy relationships with her brothers, sisters, and friends gave her a balanced perspective.

This book traces her friendships and professional relationships with many of the great names of the period, both men and women. The trends of political thought, the changing manners and customs in all strata of society, in the growing America of her day, clearly affected Dr. Blackwell's life more than that of ordinary mortals. The growth of medical cults in this country and their relationship to medical practice are touched upon. There are many themes on which one could have wished to hear more. The author has tried to give a very fair picture of her heroine, of her mistakes as well as her tremendous successes. Sentimentality is on the whole successfully avoided. Elizabeth Blackwell, 1821-1910, lived a full and satisfying life, leaving a permanent imprint on the history of her time and of medicine.

MARY DEWITT PETTIT.

The author analyzes factors of the personality which are inherited and those which are the result of external influences. The modification of the thesis that the psychotherapeutic effect depends on the psychogenetic factors and that endogenic conditions are no objects for psychotherapy is discussed and illustrated in a most interesting manner. Of special interest for the gynecologist might be the chapter on "Crises of Puberty." The increased psychosomatic instability of this age and the way to the development of the real psychosis is shown. The dystrophia puerperalis, a rare type of constitutional underdevelopment, is described and the treatment by hypophysis transplantation and adrenal cortex preparations discussed. Each physician should read this book.¹² However, it is not easy and the knowledge of the German language which is sufficient for the reading of the routine German textbooks is not adequate because psychoanalysis and psychotherapy increase the German vocabulary to a great extent and the new terms are difficult to translate. The extensive knowledge of the author in the different fields of science, which are reflected in this study, makes the reading of this book extremely interesting.

ROBERT TAUBER.

The preface informs the reader that the authors served in the German Air Corps Hospital in Posen from 1941 to 1945. At this time, they felt that there is a gap in the German medical literature concerning the discussions of diseases which require examination and treatment jointly by medical and surgical specialists. The resulting book¹³ refers, on pages 419 to 422, to the diseases of the female sex organs. Adnexitis, ectopic pregnancy, and the ovarian tumor with twisted pedicle, are the only conditions which are discussed in this group. Diseases which should be taken into consideration for the differential diagnosis are only enumerated but no signs or symptoms are shown which might help to establish the diagnosis. The treatment of pelvic inflammatory disease does not even mention antibiotics, although 1949 is the year of publication. This book cannot be considered as a valuable German contribution to medical literature.

ROBERT TAUBER.

¹²*Psycho-Therapeutische Studien.* By Prof. Dr. Ernst Kretschmer. 215 pages with 5 illustrations. Stuttgart, 1949, Georg Thieme. 13.50 German marks.

¹³*Gemeinsame Erkrankungen aus der Inneren Medizin und Chirurgie.* By Dr. Walther Kanert and Dr. Kurt August Koelsch. 500 pages with 49 illustrations. Stuttgart, 1949, Georg Thieme.

This book,¹⁴ in pocket size, describes briefly the diseases of not less than nine medical specialties and contains, in addition, chapters on diet, vitamins, hormones, diagnostic and therapeutic techniques, and an extensive list of German pharmaceutical products. Pages 97 to 125 refer to gynecology. The etiology, pathologic manifestations, diagnosis, and treatment of the conditions, which follow in alphabetical order, are discussed in condensed form. The chapter on obstetrics, pages 126 to 184, starts with the fertilization of the ovum and continues with the discussion of the signs of pregnancy, the examining technique, the prenatal care, the complications in pregnancy, the normal and abnormal delivery, and the puerperium. A valuable addition is the index at the end of the chapter on obstetrics and gynecology which enables the reader to find immediately the problem in question. The American physician, who has full command of the German language and is well acquainted with the American equivalents of German pharmaceutical products, will find in this book a helpful manual in the daily practice. Though the size of this book is small, the type is large, clear, and readily legible.

ROBERT TAUBER.

This book, **Anxiety in Pregnancy and Childbirth**,¹⁵ is the report of a study of 27 primiparous patients made between September, 1945, and June, 1946, at the Long Island College Hospital. The study was made possible through the cooperation of the Committee on Obstetrics and Gynecology of the American Psychosomatic Society and the Long Island College Hospital.

Anxiety about pregnancy or childbirth was found in every patient. Those who gave a history of much tension and anxiety prior to pregnancy carried this over into the pregnancy period, while those with little previous anxiety showed little anxiety during pregnancy. In general, say the authors, an emotionally stable woman will perform well during pregnancy. This being so, the obstetrician may anticipate that particular attention should be directed toward the emotionally unstable woman. "Recognition of and some attempt to resolve these fears at the initial visit to a prenatal clinic are important aspects in prenatal examination and care."

The viewpoint emphasized by these authors, that each delivery is a highly individualized experience and that the role of emotional factors is a highly important one, is receiving an ever-widening attention in present-day thinking. Labor, as a normal physiological experience, demands equal consideration and study to that which is recognized as abnormal. The role of emotional factors in the physiology of labor is one of highest importance because of the close association with the autonomic nervous system. This book, therefore, is a timely contribution to a subject of great interest to obstetricians everywhere. In recent years considerable interest has been aroused in the general field of medicine by the high advantages to be gained by studying the patient as a whole, as an individual. The growth of such interest in the field of obstetrics, as witnessed by the endeavor of the authors of this book, emphasizes that the obstetrician has wide and important responsibilities to his patient and as a member of society. It is predicted that the work will have wide interest and influence in the field of obstetrics.

HERBERT THOMS.

A short introduction to **Von der Angst der Kranken**¹⁶ shows the nature of fear and its effect on various organs. The usual symptoms of fear, pallor, palpitation, and perspiration are discussed, as well as the rare and more uncommon reactions and the statements supported by an extensive bibliography. Patients are very frequently apprehensive of the physi-

¹⁴**Taschenbuch der Praktischen Medizin.** By Dr. J. Kottmaier, 790 pages. Stuttgart, 1949, Georg Thieme. 24 German-marks.

¹⁵**Anxiety in Pregnancy and Childbirth.** By Henriette R. Klein, M.D., Associate in Psychiatry, Columbia University College of Physicians and Surgeons, New York, Howard W. Potter, M.D., Professor of Psychiatry, Long Island College of Medicine, Brooklyn, and Ruth B. Dyk, M.S., Research Department, New York City Youth Board. 111 pages. New York, 1950, Paul B. Hoeber, Inc. \$2.75.

¹⁶**Von der Angst der Kranken.** By Prof. Dr. Karl Scheele, 76 pages. Stuttgart, 1949, Georg Thieme. 4.80 German marks.

cal examination and alarmed by the suggestion of hospitalization and operation and the physician is supposed to respect this anxiety which is often nothing else but the fear of the unknown, and to calm the patient with a few informative and encouraging words. The author discusses the danger of medical reviews in newspapers and magazines which do not increase the knowledge of the reader but offer only superficial information resulting in untoward criticism of his physician who will not use the "most modern" procedures in his own case. The advantage of the cancer propaganda in order to enable the physician to make an early cancer diagnosis is frequently offset by the disadvantage of developing carcinophobia, by which the patient consults one physician after another and does not believe that he is in good health. Surgeons are too often in the limelight of criticism; favorable as well as unfavorable conditions which follow surgery frequently are considered as the results of the operation, even if there is no causal but only a temporal relation.

Physicians who are familiar with the German language will enjoy reading this little book which illustrates the role of the physician in overcoming the patient's anxiety complex.

ROBERT TAUBER.

The author of *Experimentelle Untersuchungen über Röntgeneffekte und chemische Effekte auf die pflanzliche Mitose*¹⁷ is a member of the x-ray department of the University at Zürich and in this monograph he is reporting his observation on the morphological changes in the mitosis of plant cells produced by radiation energy and different chemical substances. It is a detailed cytological study with numerous beautiful illustrations.

JOSEPH STASNEY.

*Fünfzig Jahre Pathologie in Deutschland*¹⁸ is written for the occasion of the fiftieth anniversary of the German Pathological Society which was founded by Rudolph Virchow. The book contains numerous interesting historical and biographical data reflecting the golden years of German medical knowledge under the stimulating leadership of many eminent physicians.

JOSEPH STASNEY.

The author of *Schilddrüse und Basedow*¹⁹ undertook an extensive study of the histological changes in the thyroid glands of wild animals (rabbits, mice, squirrels, and moles). These animals were killed after being hunted, or were trapped and kept in captivity for a short time. The histological findings of the thyroid had to be correlated with numerous variable factors such as seasonal variations, age, sex, degree and duration of fright, etc. The stimulation of the vegetative nervous system was found to be important in the thyroid function and changes in the histologic picture. The wild rabbits and mice were found to possess a highly stimulated vegetative nervous system and the severe fright and shock during the game produced an acute hyperthyroidism which was similar to Basedow's or Graves' disease observed in human beings. According to the author this hyperthyroidism appeared rather suddenly during the chase of wild rabbits as a result of the terrific fright and the changes in the histological picture may appear in thirty minutes with complete disappearance of colloid and this was followed by hyperplasia of the epithelium.

The author feels that similarly severe psychical trauma in certain constitutionally predisposed persons can produce a Graves' disease.

JOSEPH STASNEY.

¹⁷*Experimentelle Untersuchungen über Röntgeneffekte und chemische Effekte auf die pflanzliche Mitose.* By Dr. med. Kurt Hohl. 87 pages with 30 microphotograms and tables. Stuttgart, 1949, Georg Thieme.

¹⁸*Fünfzig Jahre Pathologie in Deutschland.* By W. Fischer and Georg B. Gruber. 334 pages with 2 illustrations. Stuttgart, 1949, Georg Thieme.

¹⁹*Schilddrüse und Basedow: Beiträge zur Histo-Morphologie und Function der Schilddrüse verschiedene freilebender Tiere.* By Prof. Dr. med. Wilhelm Eickhoff. 127 pages with 42 illustrations. Stuttgart, 1949, Georg Thieme.

This two-volume work **Operative Technic**²⁰ is one of the outstanding contributions to the writing on the subject in recent years. It is unique in many ways. There are no discussions or illustrations of obsolete procedures that seem to occupy so much space in ordinary texts on operative surgery. Each section is written by a surgeon of outstanding accomplishment in the field about which he writes. By such a selection of authors, even the most recently developed procedures receive a firsthand discussion from an authoritative source. There is little of hearsay and quotation in these volumes. The author simply tells you what technique he has found most effective for each individual problem. The descriptions are detailed and the illustrations profuse.

The importance of fundamental surgical principles in any technical approach is stressed in the first volume on general surgery. A basic knowledge of anatomy and physiology plus an understanding of indications and precautions is looked upon as an essential part of technical perfection. Volume I covers technical surgery of the various organs and systems ordinarily included in the realm of general surgery.

In addition many specialties including orthopedics, neuro-surgery, plastic surgery, urology, thoracic surgery, and gynecology are presented in the second volume. The section on gynecology is outstanding. Throughout an attempt is made to give the simplest indication for the use of each operative procedure. Those procedures found most useful in ordinary gynecological practice are described. In this section especially, one senses the importance of training in general surgery as a background to carrying on the surgery in a special field. Dr. Meigs illustrates this well in his radical approach to the problem of carcinoma of the uterus—extensive en masse resection of the iliac and pelvic nodes, and, for women with localized spread to the bladder, a cystectomy and ureterosigmoidostomy. Gynecologists and urologists without this point of view and training hesitate to be so radical and thereby compromise with less extensive procedures.

LLOYD W. STEVENS.

Dr. Mead is an anthropologist and psychologist, and approaches her subject, therefore, from the combined point of view of those two specialties. She has spent some fourteen years in living among and giving detailed study to seven South Sea peoples. The Samoans, the Manus, the mountain Arapesh, the cannibal Mundugumor, a river people, the lake-dwelling Tchambuli, the Iatmul head-hunters, a river people, and the Balinese. In this book **Male and Female**,²¹ she has carefully tried to evaluate the effect of adult behavior on the growing child and infant in relation to learning concerning sex. She traces in detail the differences and similarities in the roles assigned to each sex by these different island peoples. Many interesting points are brought out, but, because of the tremendous detail and the comparison between all seven peoples on each point, the result is somewhat confusing to the average reader.

Part I, of 47 pages, is devoted to an explanation of the author's approach to her subject. Part II concerns the South Sea peoples mentioned above. Part III concerns the problems of Society with an effort to make the transition between the primitive peoples and our modern civilization. Part IV concerns the two sexes in contemporary America.

Dr. Mead's approach is not partisan or critical in the deleterious sense. She is trying to give the reader insight into normal behavior and the consequences of various taboos and limitations imposed by modern living. She feels very strongly that the special aptitudes of each sex should be encouraged and that each human being should develop to the limit of capacity. She presents no panacea to accomplish this ideal. This is a serious attempt to add to our understanding of human behavior and tends to debunk some of our current theories.

MARY DEWITT PETTIT.

²⁰**Operative Technic in General Surgery and Operative Technic in Specialty Surgery.** By Warren H. Cole, M.D., Professor and Head of Department of Surgery, University of Illinois, College of Medicine. Director of Surgical Service, Illinois Research and Educational Hospitals, Chicago. Vol. I, 951 pages with 521 illustrations and 9 color plates. Vol. II, 725 pages with 394 illustrations. New York, 1949, Appleton-Century-Crofts, Inc. Price: Vol. I, \$14.00. Vol. II, \$16.00. (Either volume may be purchased separately.)

²¹**Male and Female.** By Margaret Mead, Anthropologist, Psychologist, Author and Lecturer, Associate Curator of Ethnology, American Museum of Natural History, New York City. 477 pages. New York, 1949, William Morrow and Company. \$5.00.

Obstetrics

The second edition of **Physiology of the Uterus**²² by Reynolds is most welcome. The subject matter has been extensively revised. The material, which deals for the most part with the dynamics of the uterus and related matters, is divided into eight sections: patterns and functions of uterine motility, including a review of the author's recent and provocative work in the human being; hormone control of the myometrium, in which are considered the maintenance of pregnancy, the myometrial response to the various hormones and mineral ions, and the physiologic basis for myometrial therapy; uterine growth, which includes a discussion of Reynolds' classical studies on growth of the distended uterus and the humoral factors which modify this growth; circulation of the uterus, including a most excellent and detailed consideration of the phenomenon of menstruation, changes in uterine and systemic circulation as the result of pregnancy, and the details of the placental exchange; metabolism of the uterus; innervation of the uterus; uterosomatic relationships, including the effects of hysterectomy; and the onset of labor, with consideration of the physiological relationships at term and the changes which are known and hypothesized to occur at this time. The author has himself contributed very greatly to our knowledge of all of these subjects, and he is eminently qualified to make this detailed review. The bibliography lists some 2,500 papers.

The book is of direct interest both to clinicians and to research workers in the field of uterine physiology. The available techniques for the study of uterine physiology are outlined, and species differences are clearly indicated. Most of the pertinent data now available are critically reviewed and extensively indexed. A knowledge of the matters discussed would appear to be indispensable to the enlightened and conscientious obstetrician.

The volume is attractively bound. The paper is of excellent quality, and the type is large and easy to read.

DAVID N. DANFORTH.

The second volume of the **Atlas of Mahfouz's Obstetric and Gynaecological Museum**,²³ represents all the excellent features of its predecessor. The expectations aroused by the perusal of the first volume were fully realized in the second. The subject matter is divided into ten chapters as follows: The accidents of labor; inversion of the uterus; abnormal implantation of the ovum, antenatal and intranatal causes of fetal death; pathology of the puerperium; injuries of the female genital tract, diseases of the vulva and the vagina, venereal disease in women, and benign tumors of the uterus.

In this second volume, as in the first, the specimens of Mahfouz's Museum are beautifully illustrated with 72 illustrations in full color and over 160 in black and white. The excellence of both the drawings and the reproductions match that of the first volume. The operative specimens have an almost animated quality, so clear and vivid are the clinical, anatomical, and pathological presentation of the cases from which the specimens were removed. Descriptive captions are translated into six languages.

Although many of the specimens are veritable museum pieces, the material as a whole is nevertheless of a classic character. There are many more interesting cases than can be given in a brief review. Two rare examples seldom seen in this country may serve to illustrate the unusual material presented in the Atlas. One is that of an 11-year-old child from whom more than twenty fibromyomas were removed and who subsequently gave birth to two children. Another example is that of a newly married child who had a superior vaginorectal fistula associated with bilateral hydrosalpinx and perimetritis. Bilharziasis of the female genitals, not uncommon in Egypt, is described in detail.

²²**Physiology of the Uterus.** By S. R. M. Reynolds. Second edition. 611 pages with 67 illustrations. New York, 1949, Paul B. Hoeber, Inc.

²³**The Atlas of Mahfouz's Obstetric and Gynaecological Museum.** By Naguib Pacha Mahfouz, M.Ch., F.R.C.O.G. (Hon.), F.R.C.P. Lond., F.R.C.S. Eng. (Hon). Volume Two, Chapters XI-XVIII. Altringham, England, 1949, John Sherratt and Son.

This second volume is a worthy companion of the first and merits equally a place in the obstetrician's and gynecologist's library. The author deserves great credit for his painstaking selection and the clarity of presentation of the material. It is a unique undertaking in which author and publisher have contributed the best elements in the publication of this singular Atlas.

ISIDOR C. RUBIN.

This little book on **Artificial Insemination of the Female**²⁴ is a summary of the world literature on this problem. The first of the fifteen chapters presents the historical facts on artificial insemination. The author states that 20,000 children were born by artificial insemination in the United States. He then speaks about artificial insemination in history, mentioning that Malpighi tried it in 1600, and that Lazzaro Spallanzani successfully artificially impregnated a dog in 1779. He finds that in the year 1322 there is reported the artificial insemination of a mare. The author regards Hunter, in 1790 as the first to try this process in the human being, obtaining the semen from the husband who had hypospadias.

He claims that Sims in 1866 was the first to use intrauterine injections of sperm which produced a successful impregnation. He found that in 1911 Rohleder was able to obtain 65 cases of artificial impregnation, with 21 successes.

The other chapters deal with the problems encountered in artificial insemination in the human being, questions on the religious and social problems, sentimental reactions due to artificial insemination, and difficulties of technical problems in artificial insemination. At the end there is a rather large bibliography.

This little book contains a well-organized group of facts. The author's personal opinions are expressed, together with the opinions of many others in the world concerning artificial insemination with its moral and legal aspects. The author advises the gynecologist to consult local laws on the legality of artificial insemination especially from donors other than the husband and that every precaution must be taken to insure legal acceptance of the procedure.

The book should be in the office of every gynecologist, and is recommended highly.

MARIO A. CASTALLO.

Books Received

A Primer for Diabetic Patients. An Outline of Treatment for Diabetes With Diet and Insulin Including Directions and Charts for the Use of Physicians in Planning Diet Prescriptions. By Russell M. Wilder, M.D., Ph.D., F.A.C.P., Professor and Chief of the Department of Medicine of the Mayo Foundation, University of Minn.; Senior Consultant in the Division of Medicine, Mayo Clinic. Ninth edition, 181 pages with 7 figures and one plate. Philadelphia, 1950. W. B. Saunders Company.

Textbook of Röntgen Diagnosis. By H. R. Schinz, W. E. Baensch, E. Friedl, and E. Uehlinger. Fifth edition. Volume 1: Skeleton, Part 1. With 507 illustrations and 58 colored plates. Stuttgart, 1950, Georg Thieme. DM 66.

²⁴La Fecondazione Artificiale Nella Donna by Sebastiano DiFrancesco. 96 pages. Milano, 1949, Istituto La Casa.

Correspondence

Menstrual Molimina as a Diagnostic Sign of Pregnancy

To the Editor:

Among the most universally accepted symptoms of early pregnancy is cessation of menstruation; it is usually classified as a presumptive sign. It has seemed to the writer that this symptom becomes a more definite diagnostic aid if it is combined with a consideration of menstrual molimina.

The cause of menstrual molimina is not well understood. Most authorities describe the various types of molimina, but explanations for their appearance are not usually given. It does seem to be true that they follow ovulation, and are not seen in the case of anovulatory bleeding.

Nearly all women have some premonitory symptoms of impending menstruation. It is less usual to obtain a history of periods beginning without some forewarning. The syndrome to be detailed here depends on this fact. If a woman in the childbearing age misses a period without having had her regular moliminal symptoms, she is generally not pregnant. If she is pregnant she will almost invariably state not only that she did have these symptoms, but also that they were increased both in intensity and duration. It may be necessary to question her on this point but her memory is usually very definite, and such answers as, "Yes, I felt exactly as if I were going to menstruate for a whole week," are the rule.

This differential symptom has seemed to be very accurate, and, as it is one of the earliest presumptive signs of pregnancy, it has seemed advisable to detail it. The writer claims no originality for this description, as it has probably been noted before; however, suffice it to say that a search of the literature has failed to uncover any description of this early manifestation of pregnancy.

LOCKE L. MACKENZIE, M.D.
471 Park Avenue
New York, N. Y.

Necrology

Otto Henry Schwarz, M.D., former head of the Department of Obstetrics and Gynecology of the Washington University School of Medicine, died in his home in St. Louis, on August 19, 1950, at the age of 62, after a long illness. He was born in St. Louis, June 15, 1888, the son of the late Dr. Henry Schwarz, who founded the obstetric service at Washington University some seventy years ago and whom this son later succeeded.

Dr. Schwarz graduated from Smith Academy in St. Louis in 1906, then attended Yale for two years and finally received his doctor's degree from Washington University School of Medicine in 1913, where, subsequently, he became instructor, associate professor, professor and head of the Department of Obstetrics and Gynecology. He also served as attending and consultant at the St. Louis Maternity and Barnes Hospitals, and the St. Louis City Hospital. Postgraduate work abroad occupied two years of this time.

In addition to his activities as a teacher for many years, Dr. Schwarz became well known for his clinical and research studies and his contributions to the literature of his specialty were many and varied. He was a member of the Advisory Editorial Board of the JOURNAL for many years and held fellowships in the American Gynecological as well as other general and specialist societies. He served as secretary of the former from 1932-1936, was a member of its Council in 1931, and was elected Vice-President in May, 1950.

The serious illness which necessitated his retirement from active practice did not hamper his efforts to continue work in certain research problems and he continued these at his bedside until death finally terminated his labors.

Item

American Board of Obstetrics and Gynecology

The next scheduled examination (Part I), written examination and review of case histories, for all candidates will be held in various cities of the United States and Canada on Friday, Feb. 2, 1951. Application may be made until Nov. 5, 1950.

Reopening of previous application or reapplication for Part I examination similarly should be made prior to Nov. 5, 1950, whereas candidates who have successfully completed Part I and desire to reopen their applications for Part II examination may do so until Feb. 2, 1951.

New Bulletins (1950) are now ready for distribution. The new section on details of residency training programs will be of special interest to hospitals conducting such programs as well as to prospective applicants to this Board. The Board has also adopted a special form designated as the "Application for Appraisal of Incomplete Training." These forms will be forwarded upon request to prospective applicants who desire to know their current status and needs for further training.

Application forms and Bulletins are sent upon request made to:

PAUL TITUS, M.D., Secretary
American Board of Obstetrics and Gynecology
1015 Highland Building
Pittsburgh 6, Pa.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Frederick C. Irving. *Secretary*, Norman F. Miller, 1313 East Ann St., Ann Arbor, Mich. Annual meeting, May 7, 8, 9, 1951, New York City.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, Samuel A. Cosgrove, Jersey City, N. J. *Secretary*, L. A. Calkins, University of Kansas Medical Center, Kansas City 3, Kansas. Annual meeting Hot Springs, Va., September 7, 8, 9, 1950.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, Lawrence M. Randall, Rochester, Minn. *Secretary-Treasurer*, John I. Brewer, 24 West Ohio St., Chicago 10, Ill. Annual meeting to be held Thursday, Friday, and Saturday, Sept. 21, 22, and 23, 1950, at the Hotel Schroeder, Milwaukee, Wis.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President*, Lester A. Wilson, Charleston, S. C. *Secretary-Treasurer*, John C. Burwell, Jr., 416 Jefferson Bldg., Greensboro, N. C. Annual meeting, Ormond Beach Hotel, Ormond Beach, Florida, Feb. 8, 9, and 10, 1951.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, James R. Blos, Huntington, W. Va. *Secretary*, A. B. Hunt, Mayo Clinic, Rochester, Minn. Annual meeting June, 1951, Atlantic City, N. J.
- New York Obstetrical Society.** (1863) *President*, R. Gordon Douglas. *Secretary*, Charles M. McLane, 33 East 68th St., New York 21, N. Y. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, James P. Lewis. *Secretary*, George A. Hahn, 255 S. 17th St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, John I. Brewer. *Secretary*, Edward M. Dorr, 30 N. Michigan Ave., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President*, William T. Daily. *Secretary*, J. Edward Hall, 429 Clinton Avenue, Brooklyn 5, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Houston S. Everett. *Secretary-Treasurer*, W. Drummond Eaton, 11 E. Chase St., Baltimore 2, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** (1876) *President*, Edward Friedman. *Secretary*, Robert R. Pierce, 116 William Howard Taft Road, Cincinnati 19, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Rudy F. Vogt. *Secretary-Treasurer*, Glenn W. Bryant, Louisville, Ky. Meetings fourth Monday of each month from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Ronald Frazier. *Secretary-Treasurer*, Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, Eugene A. Conti. *Secretary*, David Katz, 130—7 Avenue, Pittsburgh 22, Pa. Meetings, first Monday of each month, October to May.
- Obstetrical Society of Boston.** (1861) *President*, Roy J. Heffernan. *Secretary*, Francis Rouillard, 1180 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Arthur E. G. Edgelow, Springfield, Mass. *Recorder*, Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Philip H. Arnot. *Secretary-Treasurer*, R. Glenn Craig, 490 Post St., San Francisco, Calif.
- Washington Gynecological Society.** (1933) *President*, J. Bay Jacobs. *Secretary*, Allan E. King, 915 19 Street, N.W., Washington, D. C. Fourth Saturday, October, November, January, March, May.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, Conrad G. Collins. *Secretary*, E. W. Nelson, 1407 S. Carrollton Ave., New Orleans, La. Meetings held October, November, January, March, and May.
- St. Louis Gynecological Society.** (1924) *President*, T. K. Brown. *Secretary*, J. Russell Vaughan, 634 North Grand Blvd., St. Louis 3, Mo., Regular meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, Donald Dallas. *Secretary*, Donald W. de Carle, 2000 Van Ness Ave., San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, Howard O. Smith, Marlin, Texas. *Secretary*, George F. Adam, 4115 Fannin St., Houston 4, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, O. W. Picard. *Secretary*, Carl F. Shelton, 910 David Broderick Tower, Detroit 26, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Central New York Association of Gynecologists and Obstetricians.** (1938) *President*, Nathan N. Cohen. *Secretary*, Merton C. Hatch, Medical Arts Bldg., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.
- Alabama Association of Obstetricians and Gynecologists.** (1940) *President*, M. Y. Dabney. *Secretary*, Buford Word, 929 South Twentieth Street, Birmingham, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Robert K. Plant. *Secretary-Treasurer*, Gerald F. Thomas, 1427 Medical and Dental Bldg., Seattle 1, Wash. Meetings held on third Wednesday of each month, Washington Athletic Club.
- Denver Gynecological and Obstetrical Society.** (1942) *President*, Edward L. Harvey. *Secretary-Treasurer*, Jack M. Simmons, Jr., 804 Republic Bldg., Denver 2, Colo. Meetings held first Monday of every month from October to May (inclusive).
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, J. W. Prentice. *Secretary-Treasurer*, Alice D. Watts, 324 East Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, D. Dalton Deeds. *Secretary*, Jesse A. Rust, Jr., 3115 University Ave., San Diego 4, Calif. Meetings held on the last Friday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, W. H. Gilsdorf, Valley City. *Secretary-Treasurer*, C. B. Darner, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, Richard B. Nicholls. *Secretary*, Chester D. Bradley, 2914 West Avenue, Newport News, Va.
- Columbus Obstetric and Gynecologic Society.** (1944) *President*, Wayne Brehm. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.
- Naussau Obstetrical Society.** (1944) *President*, Robert S. Millen. *Secretary-Treasurer*, Peter La Mariana, Williston Park, L. I., N. Y. Meetings, bimonthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, Charles W. Frank. *Secretary*, Benjamin Karen, 1100 Grand Concourse, New York 56, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, Charles Kimball. *Secretary-Treasurer*, E. Gerald Layton, 805 Medical and Dental Bldg., Seattle 1, Wash. Meetings first Saturday in April and second Saturday in September.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, Richard B. Schutz. *Secretary*, William C. Mixson, 320 W. 47th St., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, A. M. McCausland. *Secretary-Treasurer*, Gordon Rosenblum, 6333 Wilshire Blvd., Los Angeles 36, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Wallace B. Bradford. *Secretary*, Richard B. Dunn. Meetings semiannually.
- The Society of Obstetricians and Gynecologists of Canada.** (1944) *President*, H. B. Atlee. *Secretary*, K. M. Grant. Annual meeting, June, 1950.
- Akron Obstetrical and Gynecological Society.** (1946) *President*, H. H. Gibson. *Secretary-Treasurer*, E. A. Riemenschneider, Second National Bldg., Akron 8, Ohio. Meetings held third Friday of January, April, July, and October, City Club of Akron, Ohio Bldg.
- Minnesota Obstetrical and Gynecological Society.** *President*, Russell J. Moe. *Secretary*, John Haugen, 100 E. Franklin, Minneapolis, Minn. Meetings held spring and fall.

- Miami Obstetrical and Gynecological Society.** (1946) *President*, Homer L. Pearson. *Secretary*, John D. Milton, 1104 Huntington Bldg., Miami, Fla. Meetings, second Thursday in January, March, May, and November.
- Omaha Obstetrical and Gynecological Society.** (1947) *President*, Ralph Luikhart. *Secretary-Treasurer*, Donald C. Vroman, 813 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.
- Oklahoma City Obstetrical and Gynecological Society.** (1940) *President*, John W. Records. *Secretary-Treasurer*, Henry G. Bennett, Jr., 800 Northeast 13 Street, Oklahoma City 4.
- Cleveland Obstetrical and Gynecological Society.** (1947) *President*, J. L. Reycraft. *Secretary*, G. Keith Folger, 10515 Carnegie Ave. Meetings on fourth Tuesday of September, November, January, March, and May at University Club, 3813 Euclid Ave., Cleveland 15, Ohio.
- New Jersey Obstetrical and Gynecological Society.** (1947) *President*, J. Carlisle Brown. *Secretary*, Harold Schwartz, 201 Lyons Ave., Newark 8, N. J. Meetings semiannually.
- Honolulu Obstetrical and Gynecological Society.** (1947) *President*, K. S. Tom. *Secretary*, S. Nishijima, 1221 Victoria St., Honolulu, Hawaii. Meetings third Monday of each month, Mabel Smyth Building.
- Oregon Society of Obstetricians and Gynecologists.** *President*, Gerald Kinzel. *Secretary-Treasurer*, Theodore M. Bischoff, 529 Mayer Bldg., Portland 5, Ore. Meetings held on third Friday of each month from October to May.
- National Federation of Obstetric-Gynecologic Societies.** (1945) *President*, Ralph E. Campbell. *Secretary*, Woodard D. Beacham, 429 Hutchinson Memorial Bldg., New Orleans 13, La.
- Dayton Obstetrical and Gynecological Society.** (1937) *President*, Albert Hirsheimer. *Secretary*, Walter K. Gregg, Dayton, Ohio. Meetings, third Wednesday monthly from September through June at the Van Cleve Hotel.
- Dallas-Fort Worth Obstetric and Gynecologic Society.** (1948) *President*, Asa A. Newsom. *Secretary*, A. W. Diddle, 2211 Oak Lawn Ave., Dallas 4, Texas. Meetings in spring and fall.
- Queens Gynecological Society.** (1948) *President*, Frederick Carpenter. *Secretary*, George Schaefer, 112-25 Queens Blvd., Forest Hills, N. Y. Meetings held second Wednesday in February, April, October, and December, at the Queens County Medical Society Bldg.
- Mississippi Association of Obstetricians and Gynecologists.** (1947) *President*, R. C. O'Ferrall. *Secretary*, William Weiner, Barnett-Madden Bldg., Jackson, Miss. Meetings held semiannually.
- Florida Obstetric and Gynecologic Society.** (1948) *President*, Robert G. Spicer. *Secretary-Treasurer*, Dorothy D. Brame, 1235 Kuhl Ave., Orlando, Fla. Next annual meeting, April, 1951, at Hollywood, Fla.
- South Carolina Obstetrical and Gynecological Society.** (1946) *President*, J. Decherd Guess. *Secretary*, Arthur L. Rivers, 231 Calhoun St., Charleston, S. C. Meetings held in spring and fall.
- Buffalo Obstetrical and Gynecological Society.** (1946) *President*, W. Herbert Burwig. *Secretary*, Clyde L. Randall, 925 Delaware Avenue, Buffalo, N. Y. Meetings held on the first Tuesday of October through May at the Saturn Club.
- El Paso Gynecological Society.** (1948) *President*, Gerald H. Jordan. *Secretary-Treasurer*, Gray E. Carpenter, 303 N. Oregon St., El Paso, Texas.
- Kentucky Obstetrical and Gynecological Society.** (1947) *President*, A. J. Whitehouse. *Secretary*, Edwin P. Solomon, 910 Heyburn Bldg., Louisville, Ky.
- Indianapolis Obstetrical and Gynecological Society.** (1947) *President*, David L. Smith. *Secretary*, Sprague H. Gardiner, 314 Hume Mansur Bldg., Indianapolis 4, Ind. Meetings held in January, April, and October.
- Houston Obstetrical and Gynecological Society.** (1939) *President*, John A. Wall. *Secretary-Treasurer*, Herman L. Gardner, Hermann Professional Bldg., Houston 5, Texas. Meetings held second Tuesday of each month except July, August, and September.
- Iowa Obstetric and Gynecologic Society.** *President*, J. H. Randall. *Secretary*, William C. Keettel, Iowa City, Iowa.
- Memphis Obstetrical and Gynecological Society.** (1950) *President*, James M. Brockman. *Secretary*, James H. Smith, 1195 Poplar Ave., Memphis 5, Tenn. Meetings, fourth Friday, October to May.
- Birmingham Obstetrical and Gynecological Society.** (1949) *President*, W. N. Jones. *Secretary*, Herbert H. Thomas, 1005 South Twenty-First St., Birmingham, Ala. Meetings four times yearly.
- Mobile Obstetrical and Gynecological Society.** (1949) *Secretary*, O. M. Otts, 1059 Dauphin Street, Mobile, Ala.